Modeling (some aspects of) the female reproductive system

Romain Yvinec

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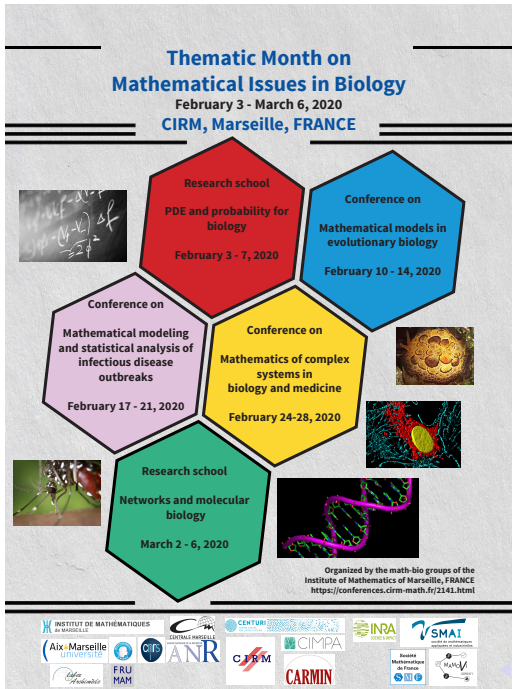
Physiologie de la Reproduction et des Comportements
INRAe Tours



Acknowledgements

- ⋆ INRIA Saclay : Frédérique Clément, Guillaume Ballif, Frédérique Robin
- ⋆ INRAE PRC : Team BIOS, BINGO (Danielle Monniaux, Véronique Cadoret, Rozenn Dalbies-Tran)
- ⋆ INRAE LPGP (Julien Bobe, Violette Thermes)
- ⋆ CEMRACS 2018 (Céline Bonnet (CMAP, X), Kerloum Chahour (U. Côte d'Azur))

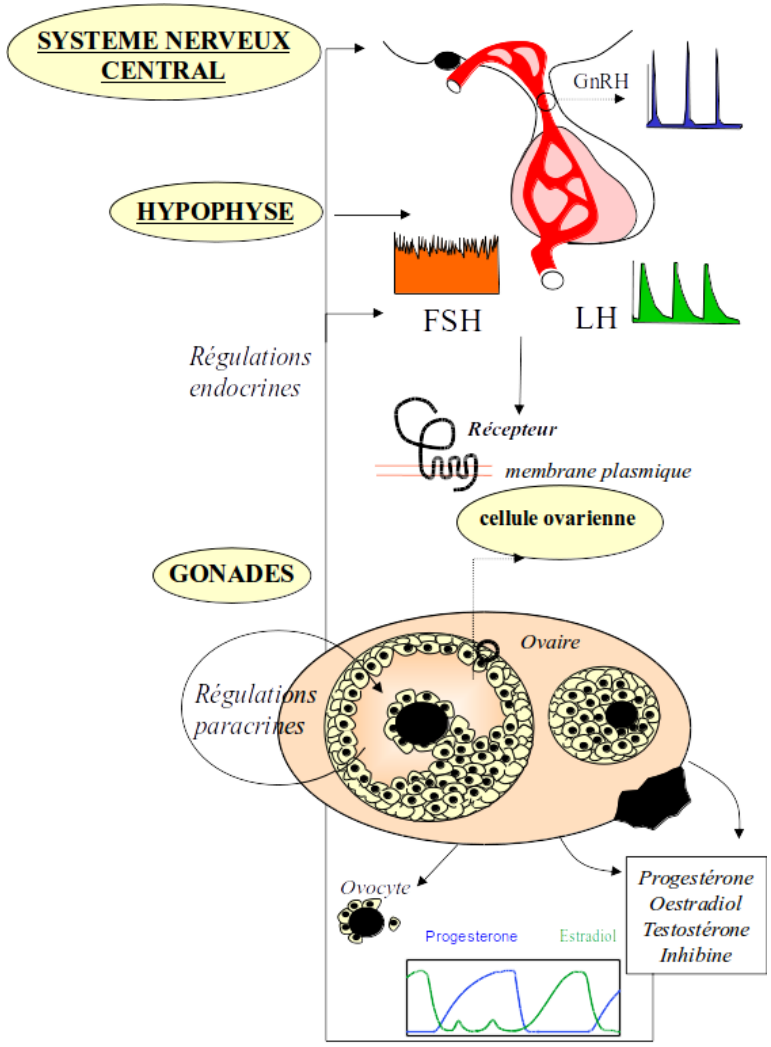
The Mammalian female reproductive system : a complex multiscale system

Encoding and decoding neuro-hormonal signals

Population dynamics : gametogenesis

Intra-cellular level : signaling networks

Yvinec et al., *Advances in computational modeling approaches of pituitary gonadotropin signaling*, Expert Opinion on Drug Discovery, 2018.



Scientific and societal issues in reproductive science

Understanding of a complex process of developmental biology, occuring during the whole lifespan

- Numerous cell types involved, and various interactions
- Many different spatial and temporal scales
- Hormonal feedback (endocrine, paracrine, autocrine)
- Steric and biophysical constraint

Preserve the reproductive ability

- Iatrogenic or physiological alterations
- Sensibility to environmental conditions
- Biodiversity preservation

Control of the reproduction function (in humans and animals)

- Biotechnology of reproduction (*in vivo*, *ex vivo*, *in vitro*)
- Clinical, economical and environmental issues

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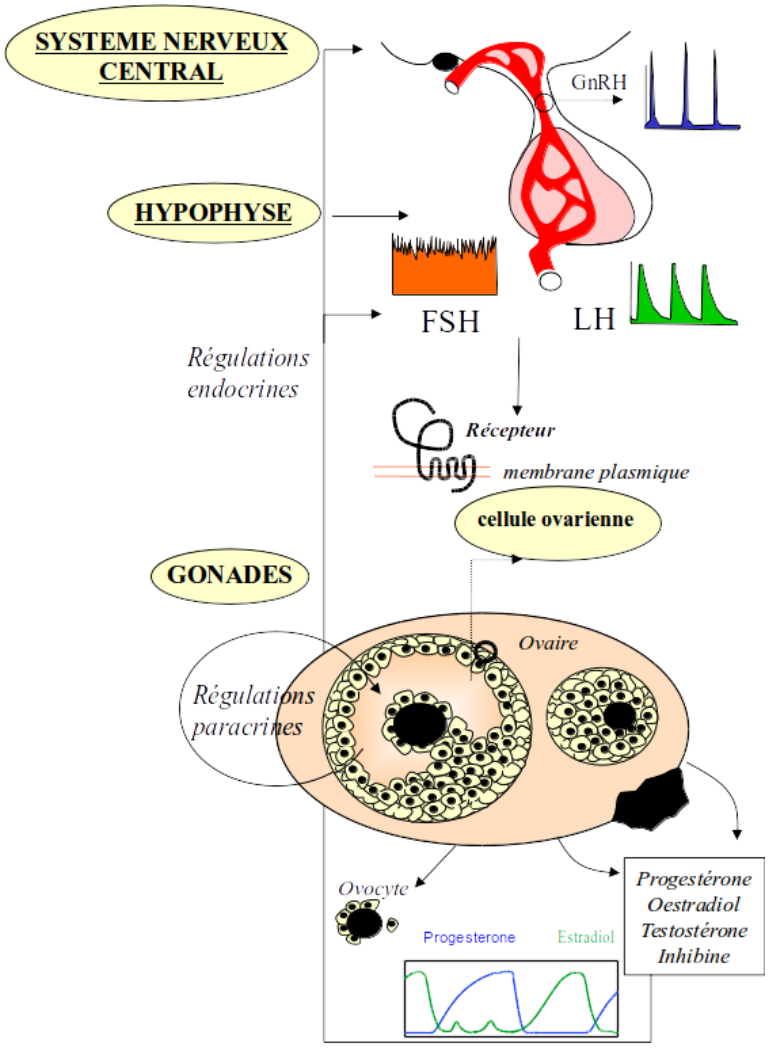

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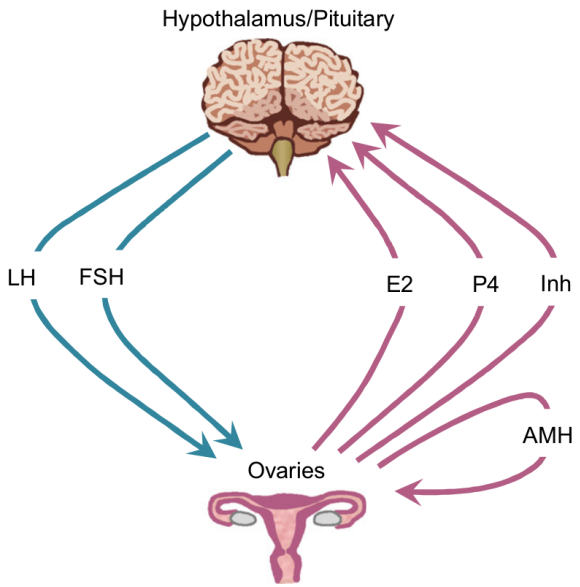
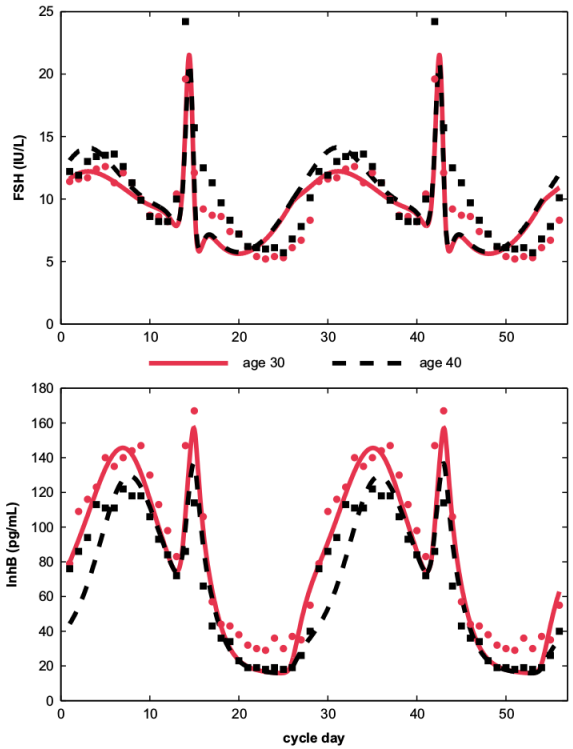
Neuro-hormonal signals (at the anatomic scale)

Mostly phenomenological equations (DDEs/SDEs) to represent measured levels of circulating hormones, on a daily basis.



Margolskee & Selgrade, JTB 2013



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These models can explain some disorders in hormonal levels and predict the effect of pharmaceutical intervention.

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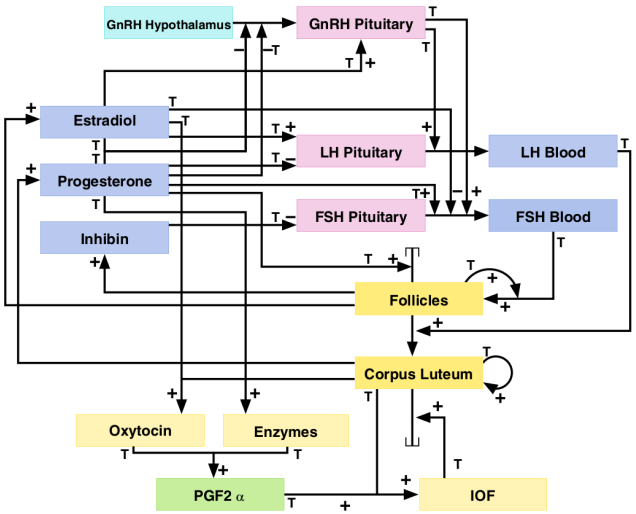
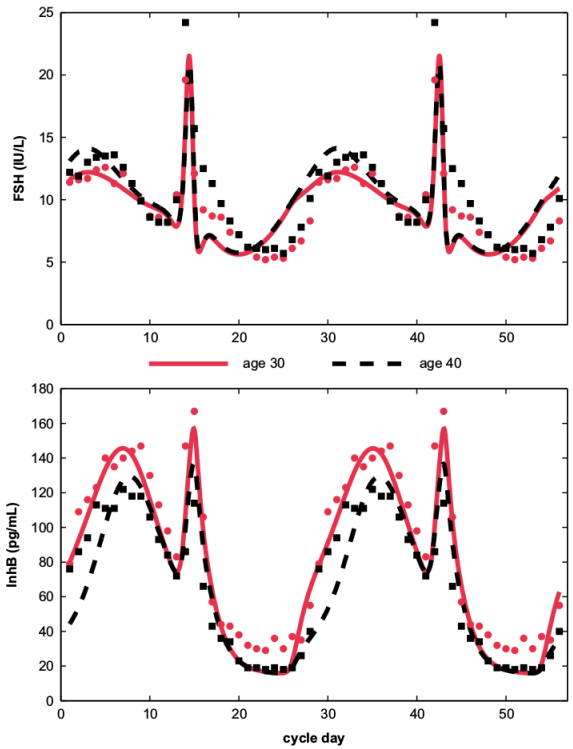


Stötzel et al., Therio. 2012



Margolskee & Selgrade, JTB 2013

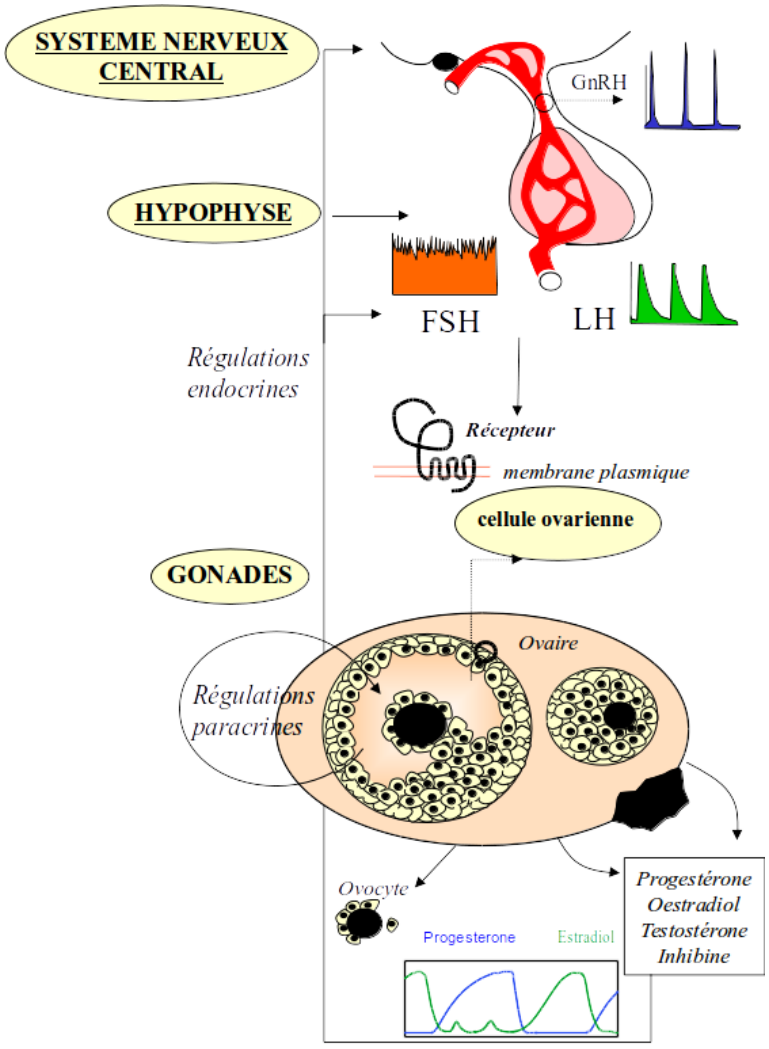
These models can explain some disorders in hormonal levels and predict the effect of pharmaceutical intervention. **Theoretical analysis gets rapidly challenging !**

The Mammalian female reproductive system : a complex multiscale system

Encoding and decoding neuro-hormonal signals

Population dynamics : gameto-genesis

Intra-cellular level : signaling net-works



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Gametogenesis : Ovarian folliculogenesis

- Morphogenesis and maturation of ovarian follicles
  somatic and germ (egg) cells
  $\Rightarrow$ Somatic cell division and germ cell growth up to ovulation

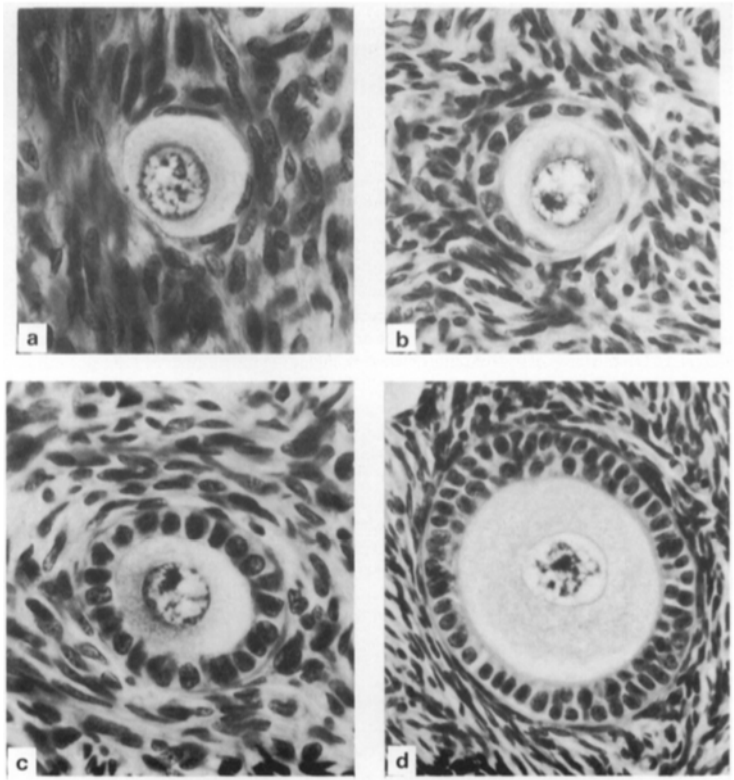

Fig. 1. Illustrations of follicle types: (a) Type B, × 570; (b) Type B/C, × 570; (c) Type C, × 570; (d) Type D, × 410.

Gougeon & Chainy, J. Reprod. Fert. 1987

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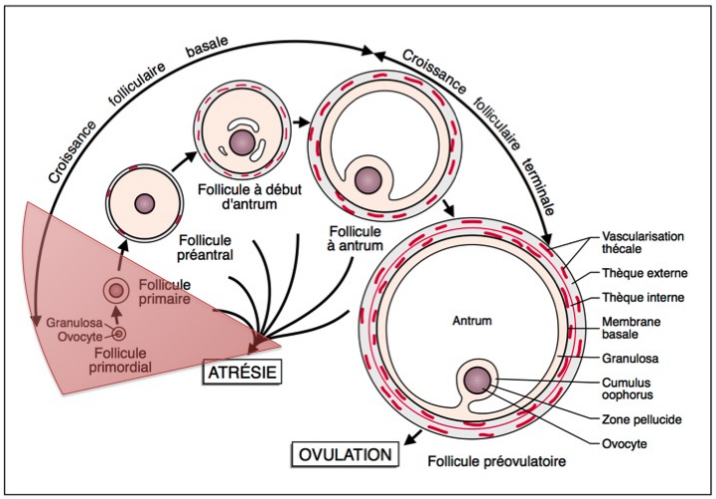
- Pool of Quiescent follicles
  static reserve (perinatal in most mammals)
  Slow activation



Monniaux, Theriogenology 2016

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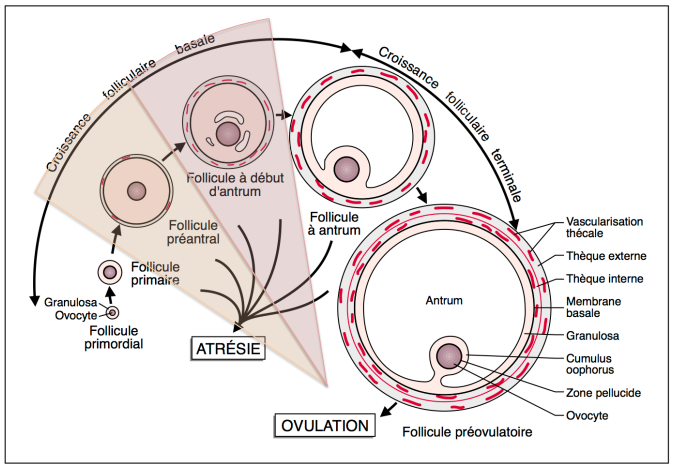

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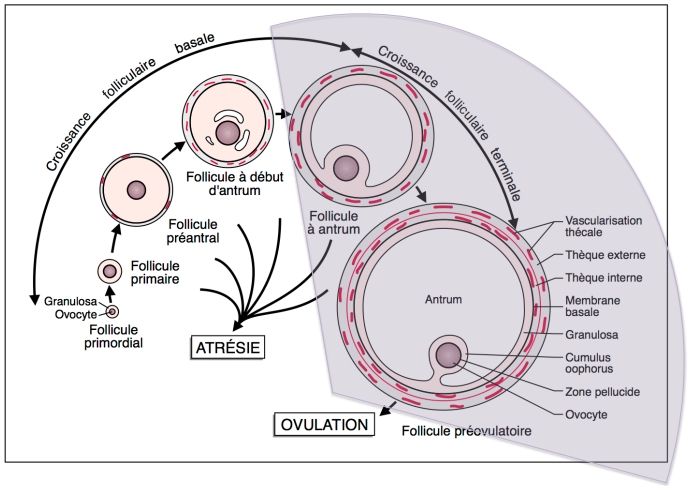

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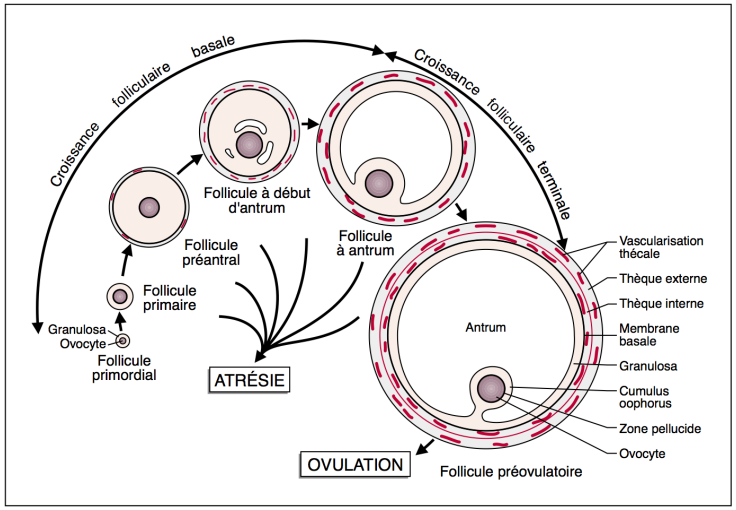
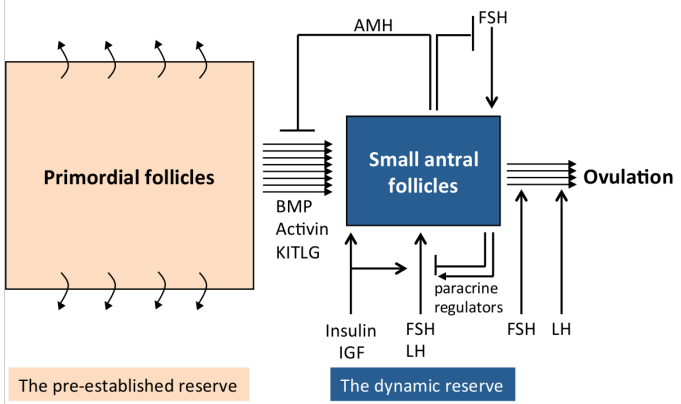
  After puberty : ovulation within an ovarian cycle
- Interactions between all follicles via complex (neuro-) hormonal signals



Ovarian reserves of follicles and their regulations



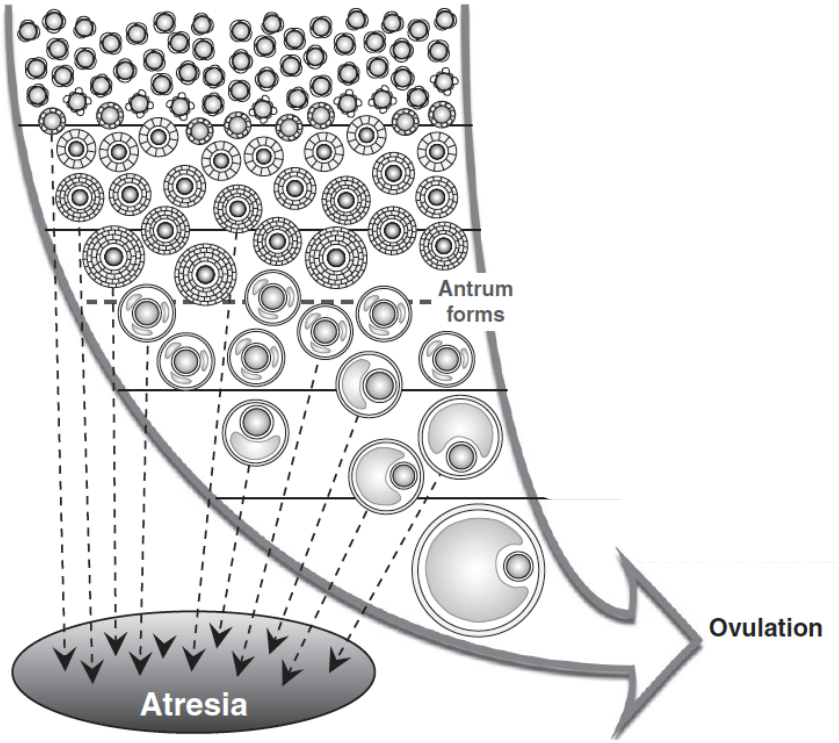
Monniaux, Theriogenology 2016

Order of magnitude

Follicle population in women

- Quiescent follicles

peri-natal	$\approx 5 \cdot 10^6$
At birth	$\approx 1 \cdot 10^6$
At puberty	$10^4 - 10^6$
At menopause	$< 10^3$
Activation rate	"A few per days"



Scaramuzzi et al., Reprod.Fert. Dev. 2011

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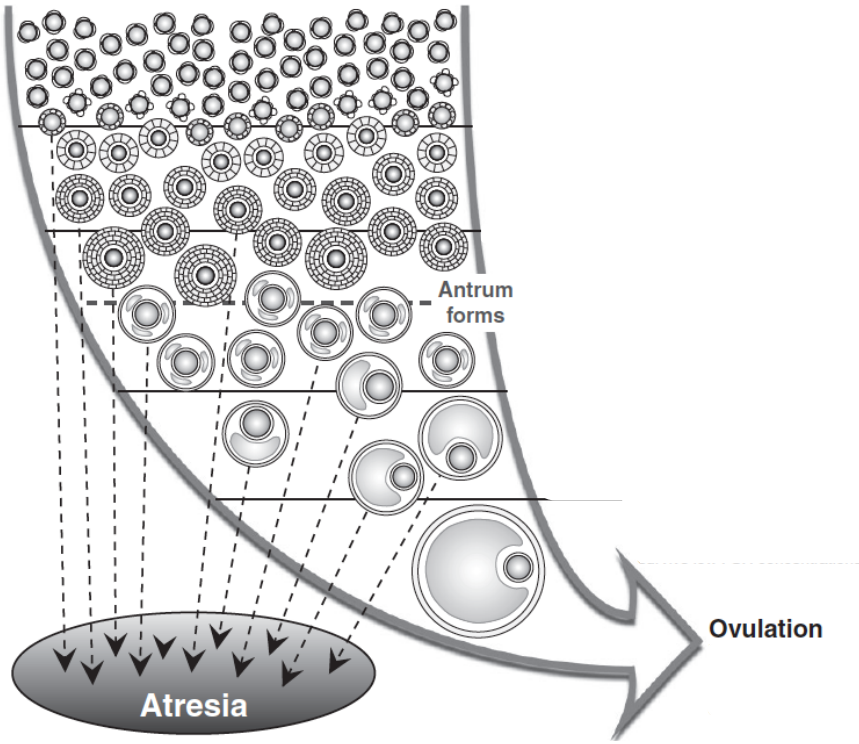
  - At birth $\approx 1 \cdot 10^6$
  - At puberty $10^4 - 10^6$
  - At menopause $< 10^3$
  - Activation rate "A few per days"
- Growing follicles
  - Maturation time $120 - 180j$
  - Basal follicles $10^3 - 10^4$
  - Terminal follicles 10^2
  - Pre-Ovulatory follicles a few
  - Atresia Most of them !



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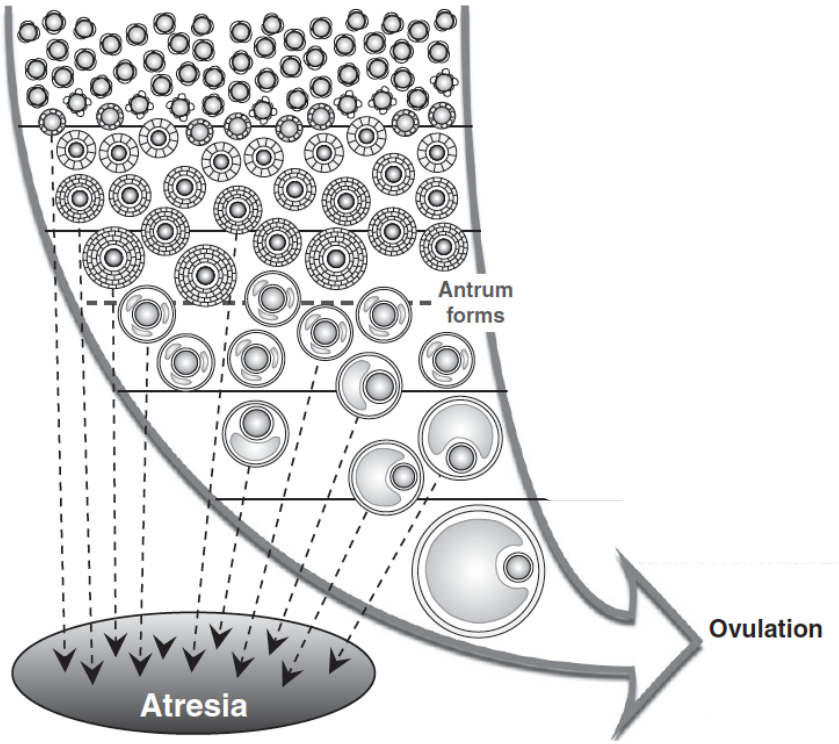
Atresia	Most of them !

-> **Only** 400 **follicles will ever reach the pre-ovulatory stage**

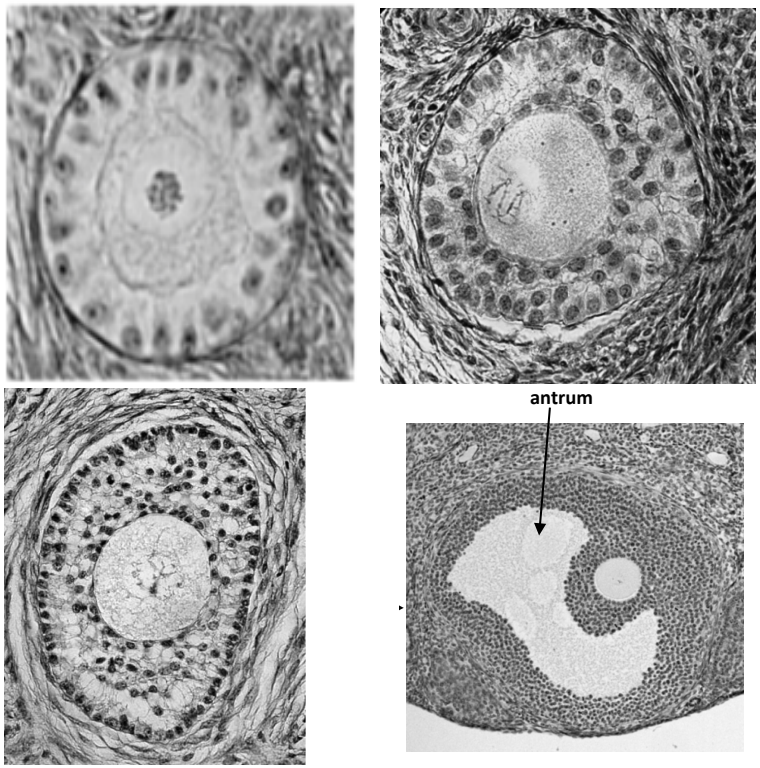


Scaramuzzi et al., Reprod.Fert. Dev. 2011

Order of magnitude

- **a single follicle (in women)**
  at different maturation stages

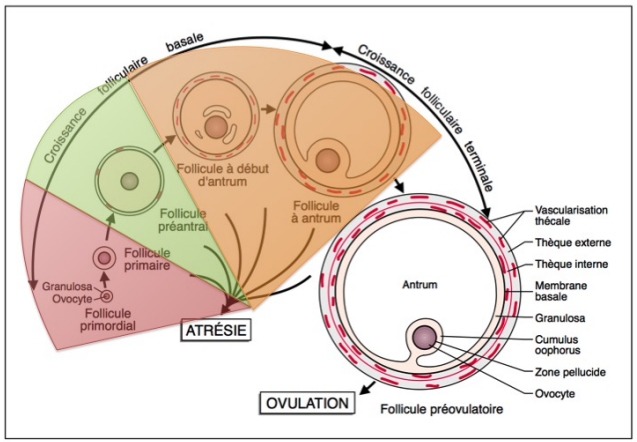
somatic cells diam.	$10\mu m$
ovocyte (egg cell) diam. :	$10 - 100\mu m$
follicle diam.	$0.03 - 20mm$
nb somatic cells	$10^2 - 10^7$



Courtesy of Danielle Monniaux.

Modeling ovarian folliculogenesis

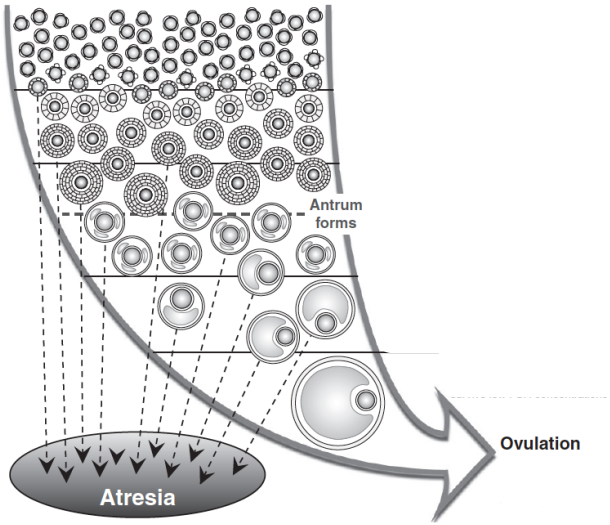
Growth of a single follicle



Monniaux et al., M/S. 1999

- Thesis of F. Robin, (co-supervised. F. Clément) 2016-2019

Populations of follicles



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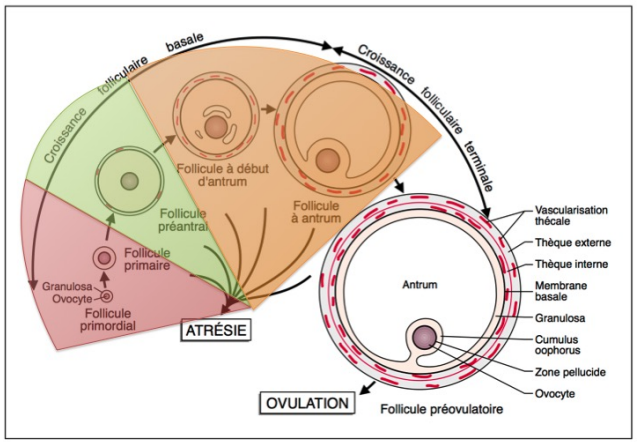

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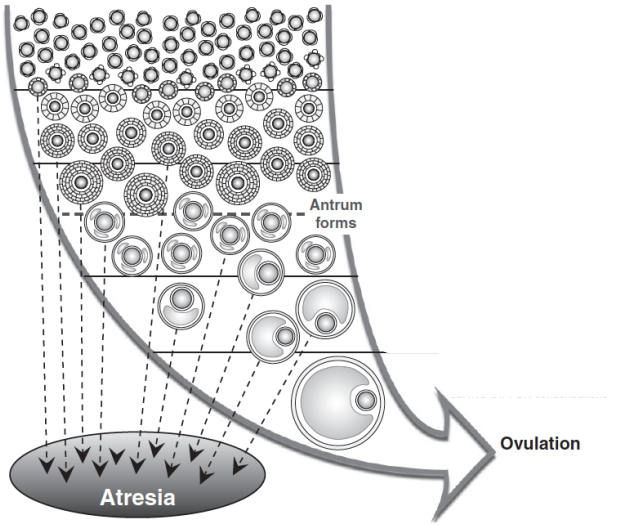

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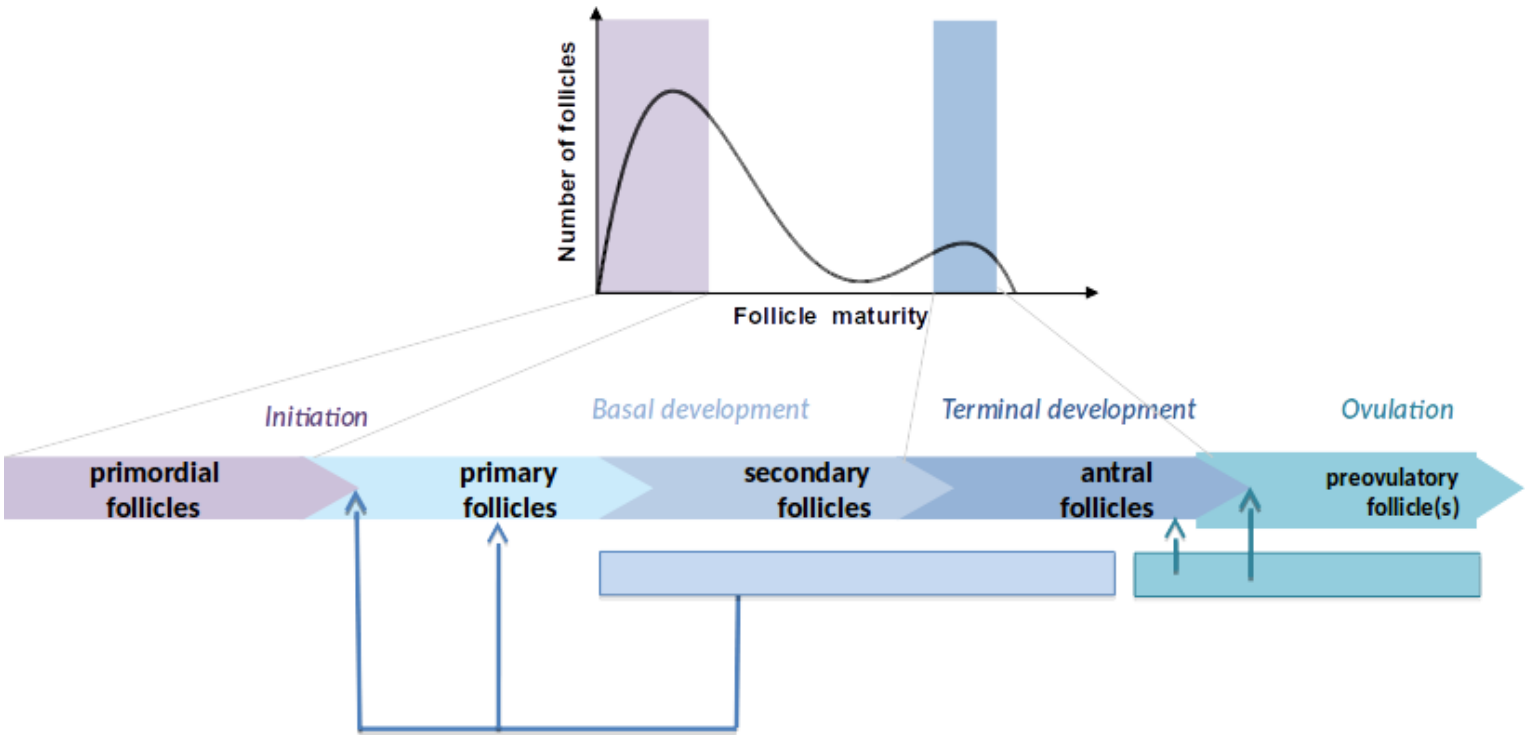
Models of population of follicles on the lifespan

⇒ Nonlinear interactions between follicles populations (endocrine and paracrine)

⇒ Slow decay of total follicles number and "stable" repartition in the maturity space



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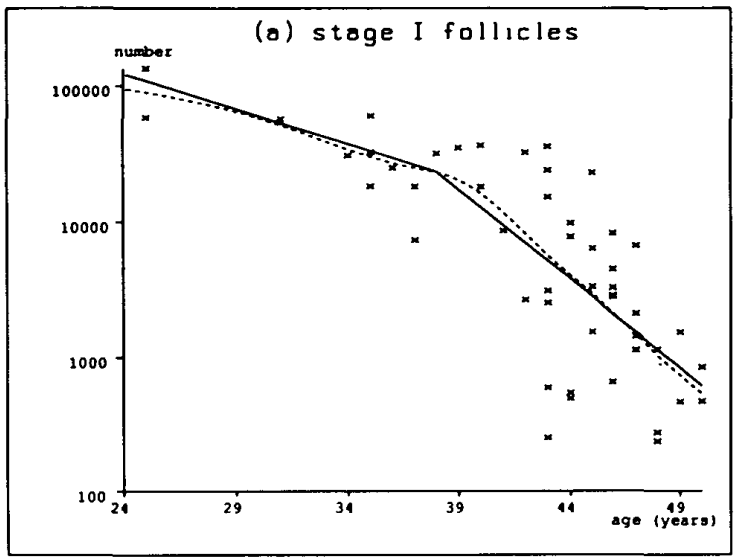

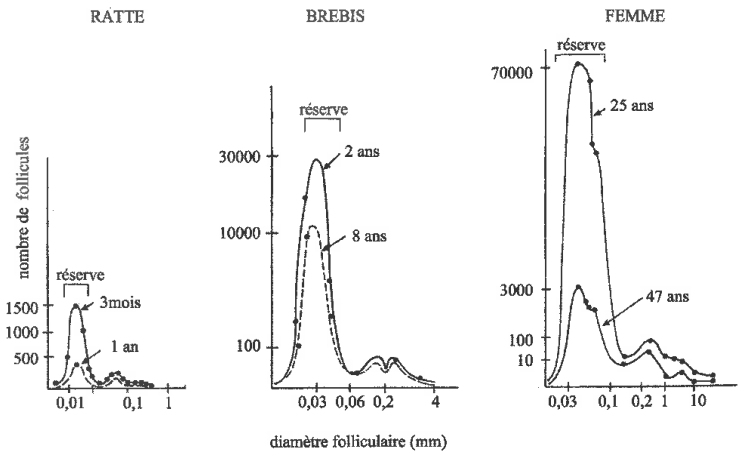

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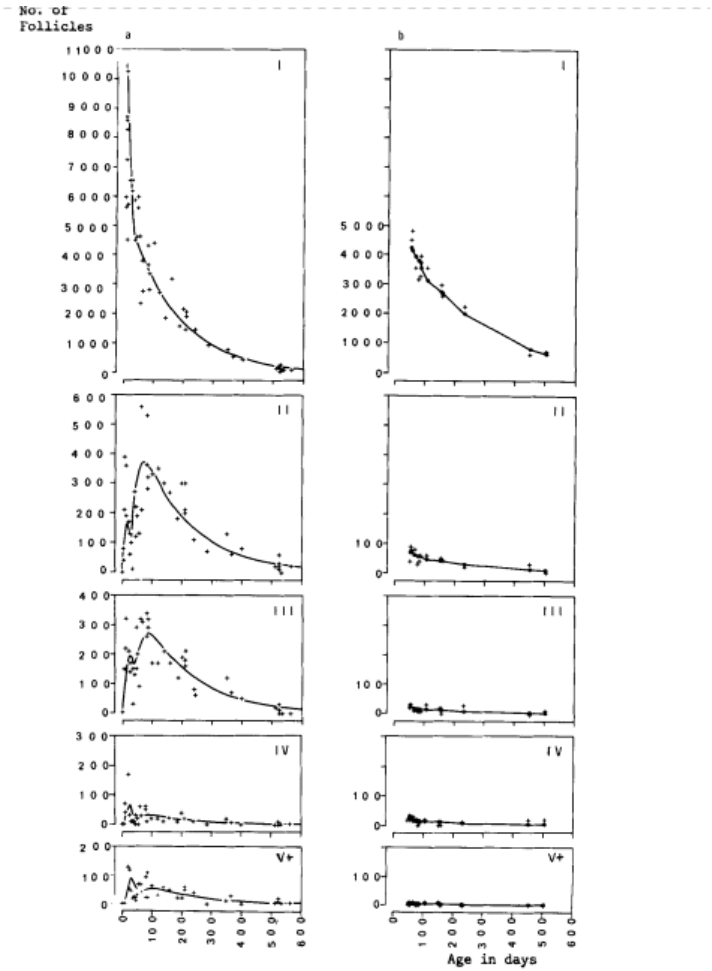
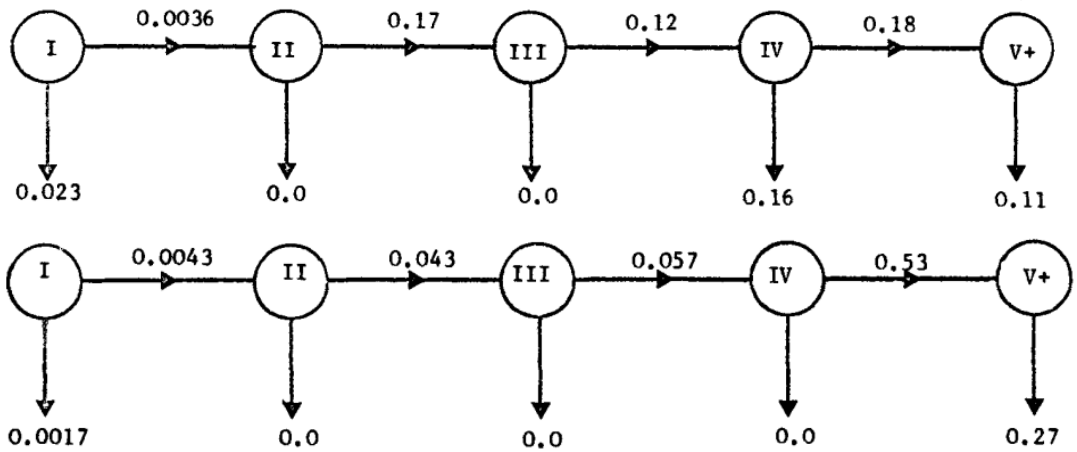


Faddy et al., J. Exp. Zool. 1976

An Analytical Model for Ovarian Follicle Dynamics

M. J. FADDY,[1] ESTHER C. JONES [2] AND R. G. EDWARDS [3]
[1] Department of Mathematical Statistics, University of Birmingham, Birmingham B15 2TT, U.K.; [2] Department of Anatomy, University of Birmingham, Birmingham B15 2TJ, U.K., and [3] Physiological Laboratory, University of Cambridge, Cambridge CB2 3EG, U. K.

- "Migration-death" stochastic model
- Linear model with time-dependent coefficient



Models of population of follicles on the lifespan

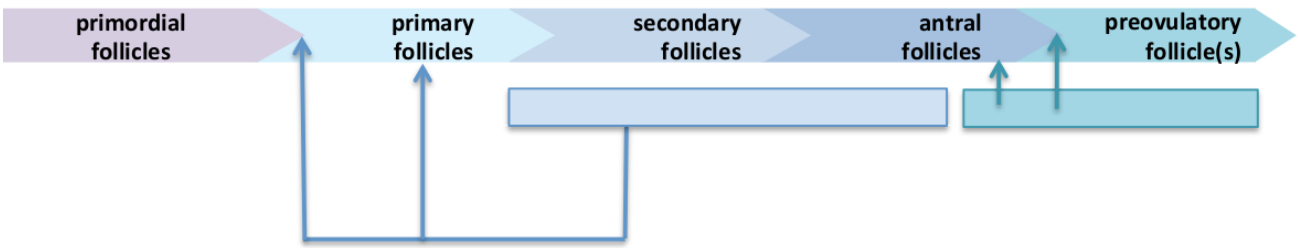
- Compartment based model (CTMC)
- Nonlinear interaction between follicles populations via $\lambda's$ and $\mu's$.
- Several time scales

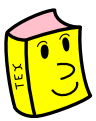
$$\lambda_i(X) = m_i + \frac{f_i}{1 + K_{1,i} \sum_{j=0}^{d} \omega_{1,j} X_j},$$

$$\mu_i(X) = g_i \left(1 + K_{2,i} \sum_{j=0}^{d} \omega_{2,j} X_j\right)$$

$$\begin{array}{ccccccccc} & & \lambda_0 & & \lambda_1 & & \lambda_2 & & \\ X_0 & \to & & X_1 & & \to & & \cdots & X_d \\ \downarrow \mu_0 & & & \downarrow \mu_1 & & & \downarrow \mu_2 & & \downarrow \mu_d \\ \emptyset & & & \emptyset & & & \emptyset & & \emptyset \end{array}$$

Initiation *Basal development* *Terminal development* *Ovulation*





Bonnet et al. *Multiscale population dynamics in reproductive biology : singular perturbation reduction in deterministic and stochastic models*, to appear in ESAIM : PROCEEDINGS AND SURVEYS.

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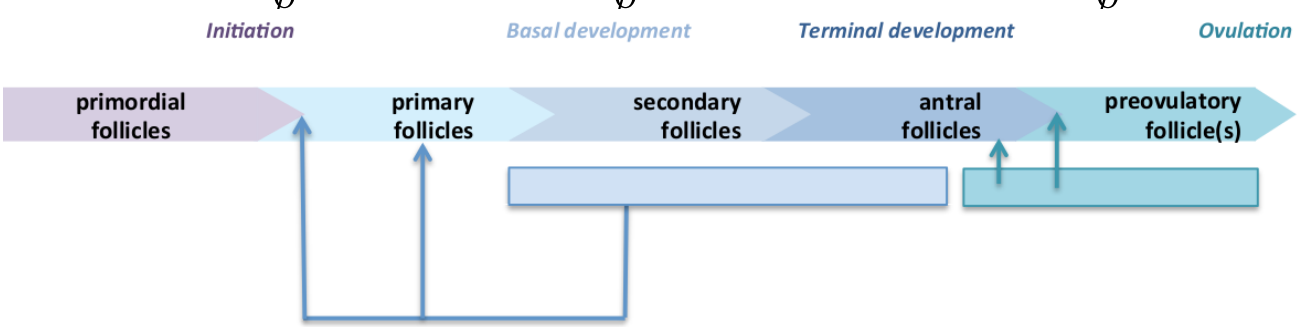

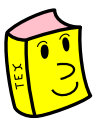

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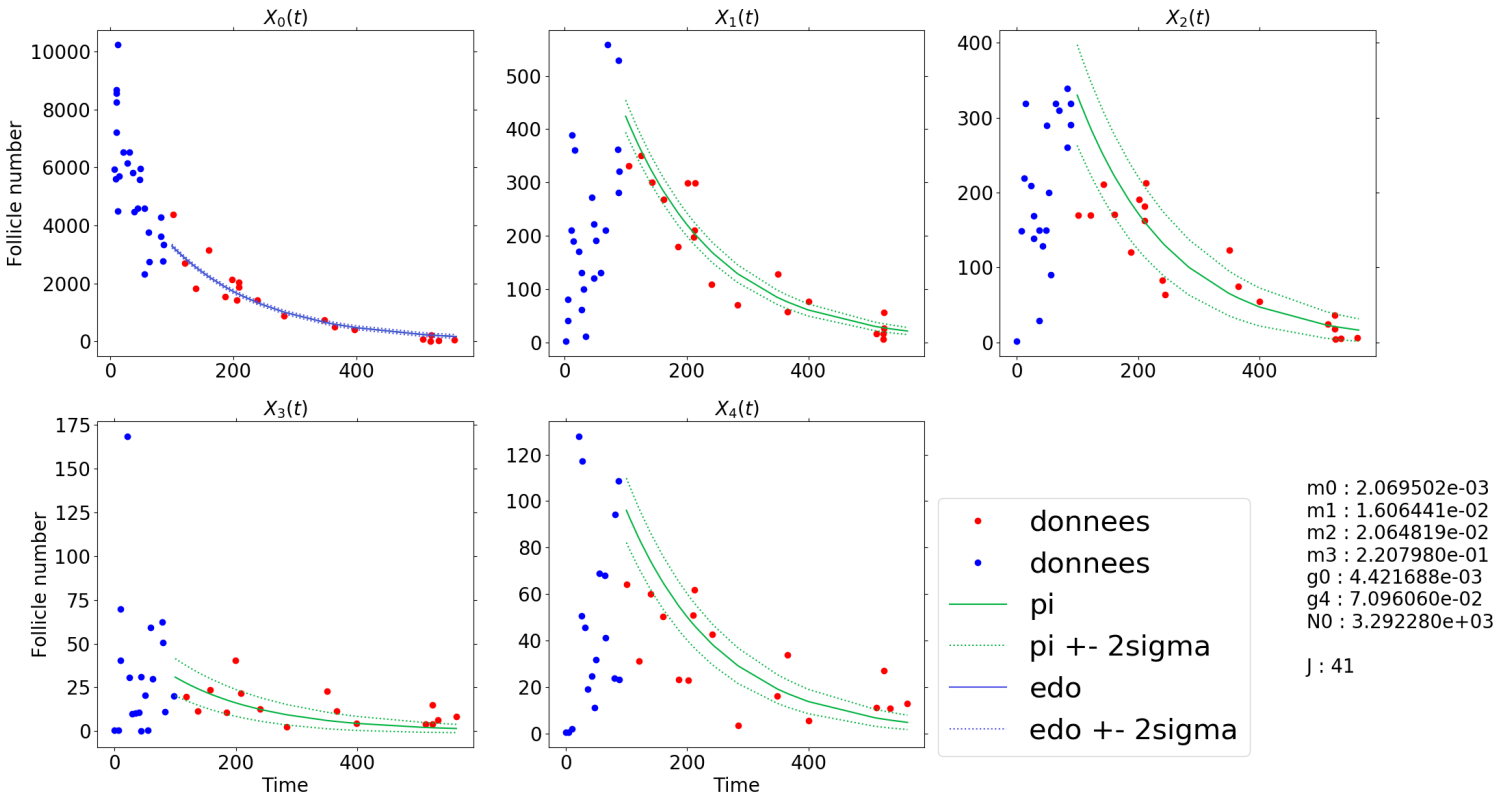
\emptyset & & & \emptyset & & \emptyset & & & \emptyset
\end{array}
$$

Theorem (G. Ballif, Averaging slow-fast dynamics)

For smooth and lower/upper bounded rates λ, μ, the CTMC converges as $\varepsilon \to 0$ (in $\mathcal{D}_{\mathbb{R}}[0,\infty[\times\mathcal{L}_m(\mathbb{N}^d)$) towards the solution of

$$
\left\{
\begin{array}{rcll}
\dfrac{dx_0}{dt}(t) & = & -\Lambda_0\big(x_0(t)\big)x_0(t) & x_0(0) = x_0^{in}, \\
\Lambda_0(x_0) & = & \displaystyle\sum_{y\in\mathbb{N}^d}\Big(\lambda_0(x_0,y)+\mu_0(x_0,y)\Big)\pi_{x_0}(y) & \forall x_0 \in \mathbb{R}_+, \\
0 & = & \displaystyle\sum_{y\in\mathbb{N}^d} L_{x_0}f(y)\pi_{x_0}(y) & \forall f \in \mathcal{C}_b^2(\mathbb{N}^d), \\
L_{x_0}f(y) & = & \lambda_0(x_0,y)x_0\Big[f(y+e_1)-f(y)\Big] & \forall y \in \mathbb{N}^d, \\
 & & \displaystyle+\sum_{i=1}^{d-1}\lambda_i(x_0,y)y_i\Big[f(y+e_{i+1}-e_i)-f(y)\Big] & \\
 & & \displaystyle+\sum_{i=1}^{d}\mu_i(x_0,y)y_i\Big[f(y-e_i)-f(y)\Big] &
\end{array}
\right.
$$

Models of population of follicles on the lifespan



- Separation of time scale is coherent with biological knowledge and follicles count data.

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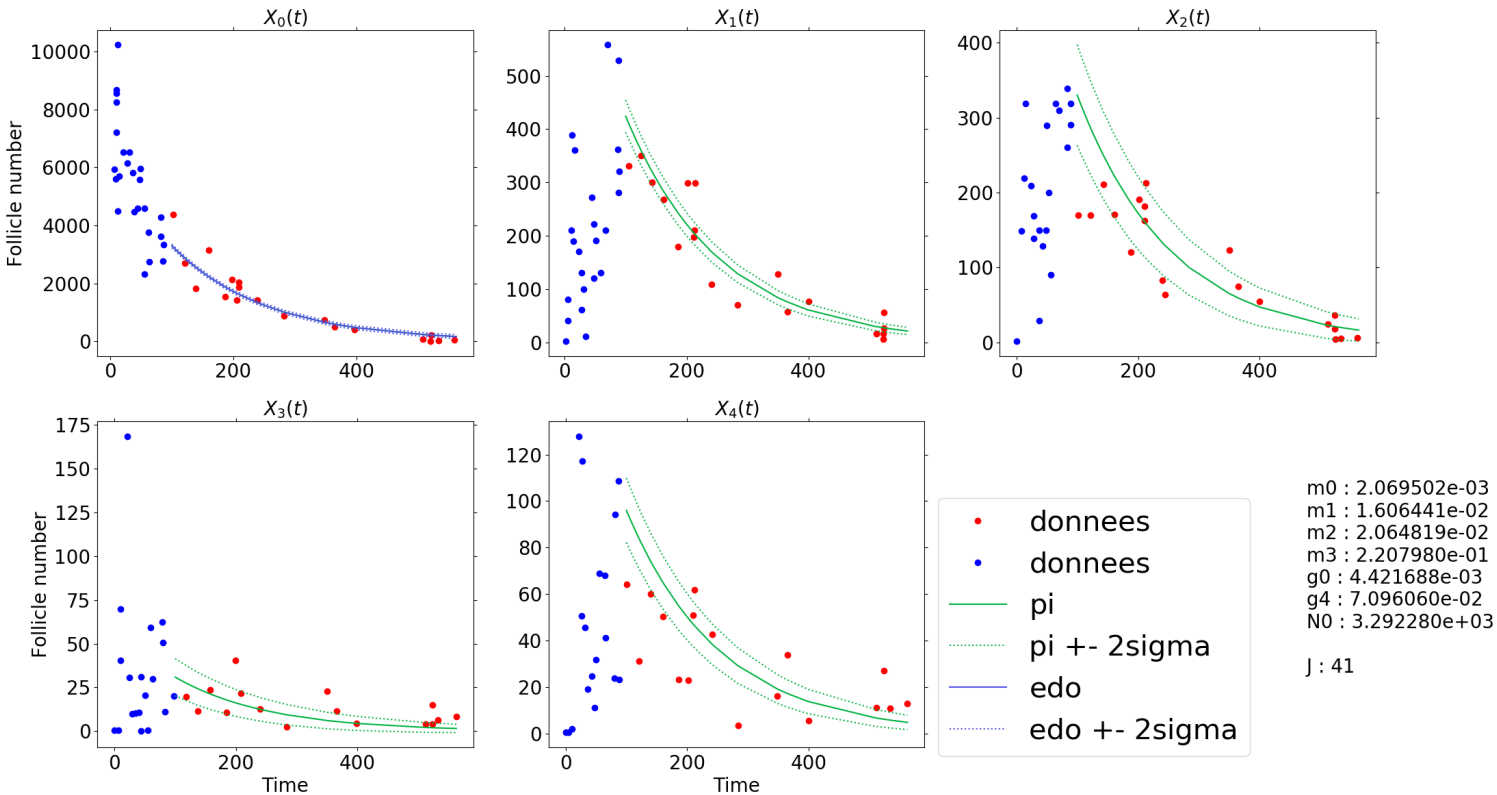
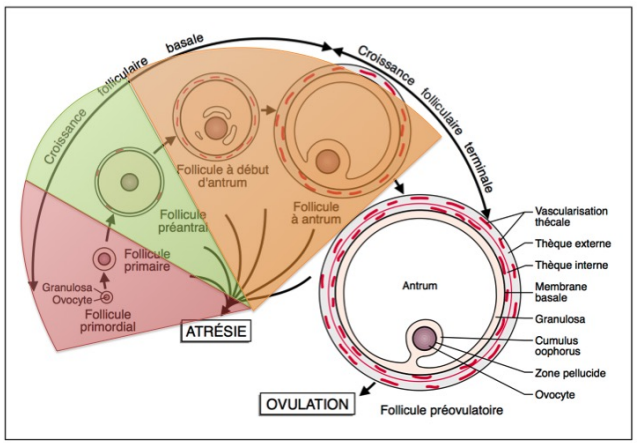


- Separation of time scale is coherent with biological knowledge and follicles count data.
- **Work in progress...**
- Identifiability issues (even with the linear model)
- The limit model allows to test null hypothesis (no regulation)

Modeling ovarian folliculogenesis

Growth of a single follicle



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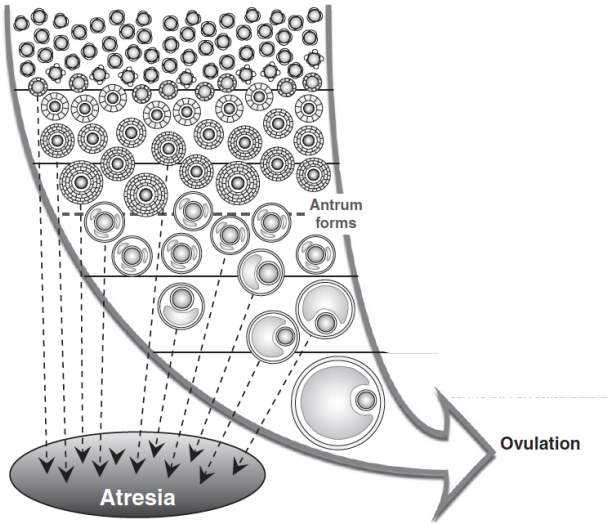
- Thesis of F. Robin, (co-supervised. F. Clément) 2016-2019

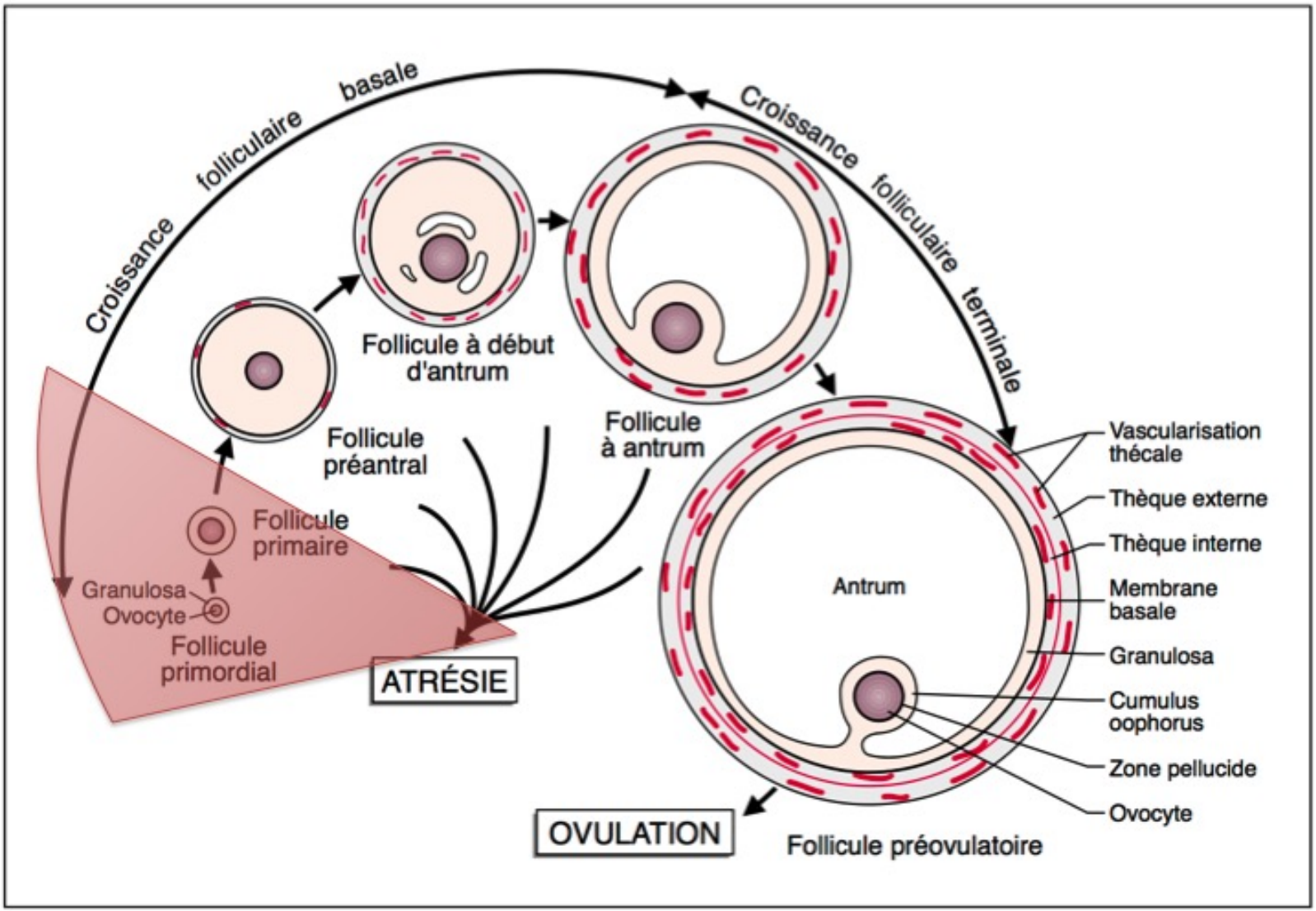
Populations of follicles



Scaramuzzi et al., Reprod. Fert. Dev. 2011

- CEMRACS 2018 (summer school), C. Bonnet, K. Chahour, (co-supervised by F. Clément, M. Postel)
- Thesis of G. Ballif, (co-supervised. F. Clément) 2019-2022

Follicle initiation



Key features of follicle initiation

- Leave the quiescent phase (static reserve)
- A single layer of somatic cells
- Two types of cells : Flattened and Cuboid
- Irreversible transition from Flattened to Cuboid cells
- The follicle is "activated" when all cells have transitioned
- **"Awakening" signals both from external and internal cues**

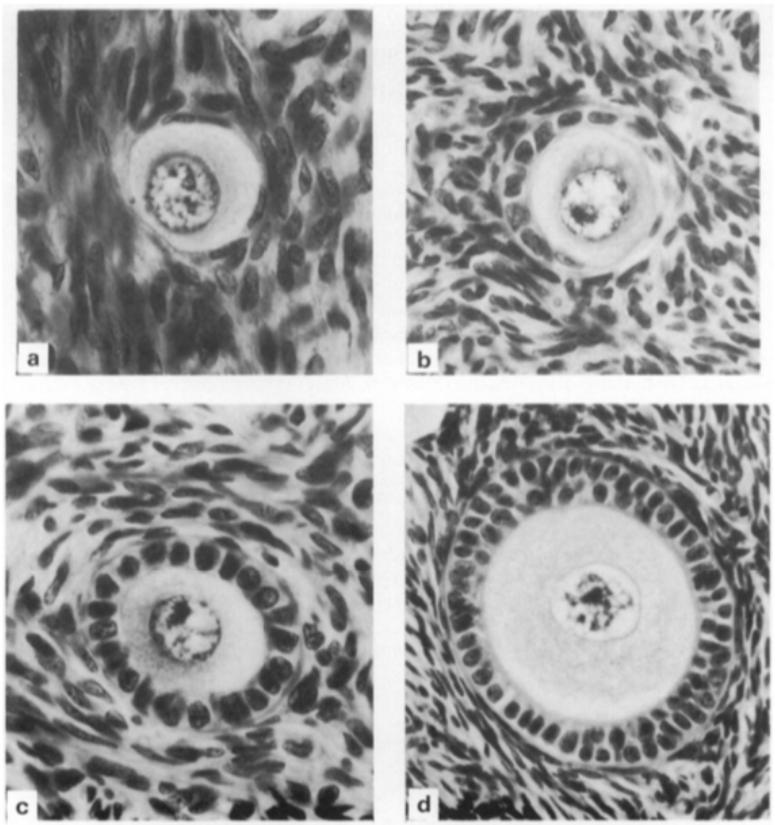
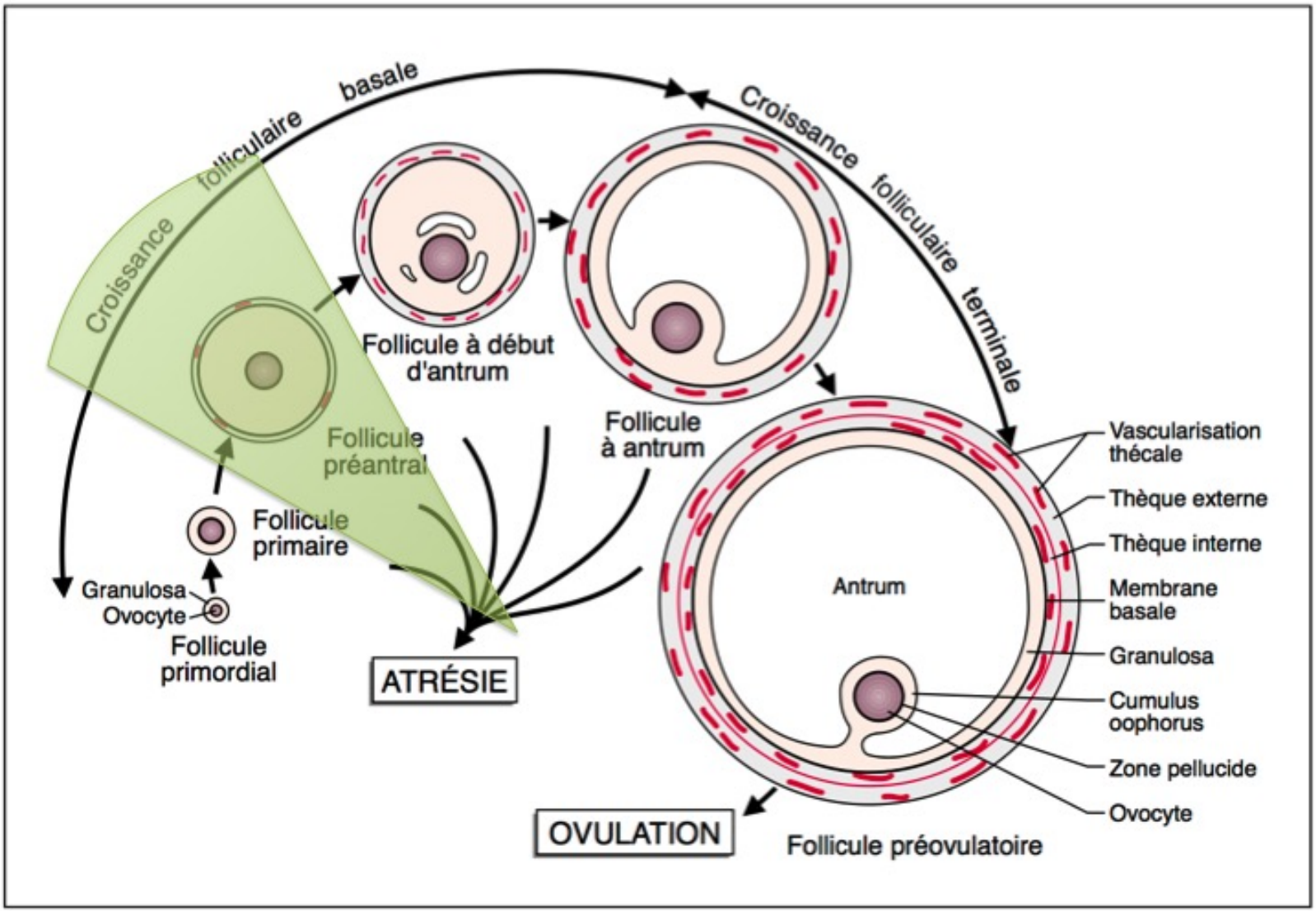


Fig. 1. Illustrations of follicle types: (a) Type B, ×570; (b) Type B/C, ×570; (c) Type C, ×570; (d) Type D, ×410.

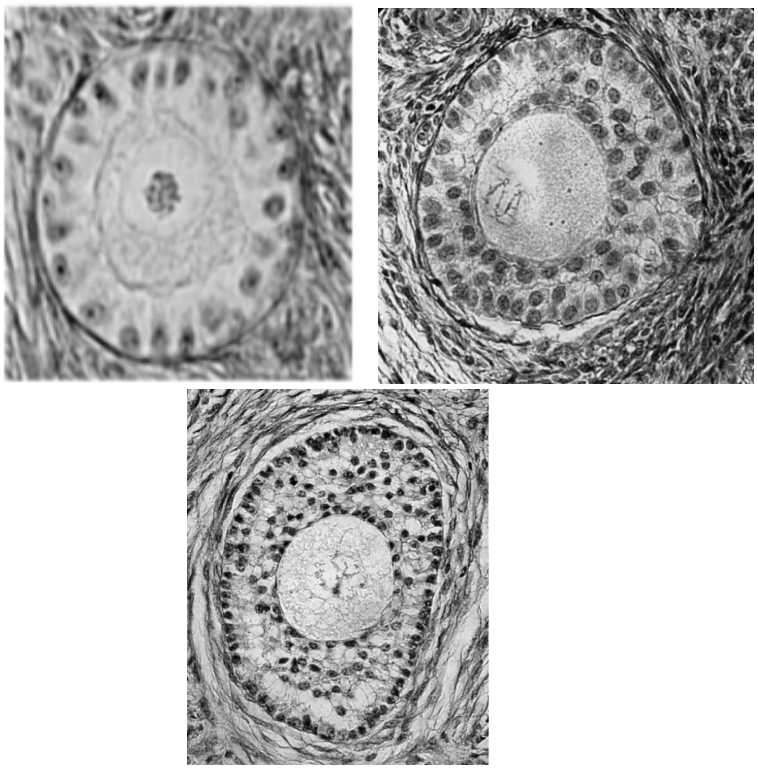
Gougeon & Chainy, J. Reprod. Fert. 1987

Basal growth



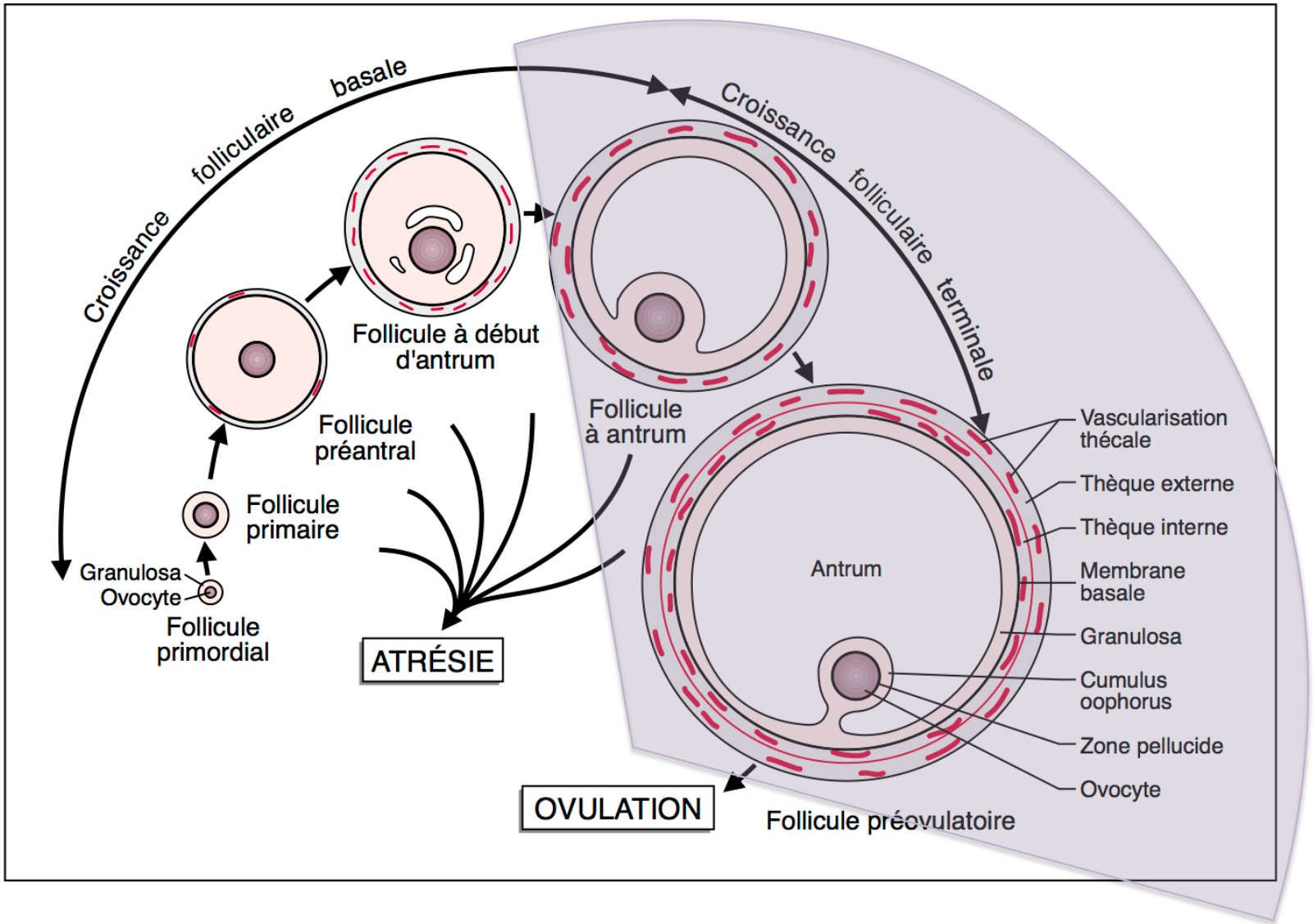
Key features of follicle basal growth

- Growth of a small follicle after initiation
- Spherical Symmetry
- Spatial structure of somatic cells in concentric layers
- Joint dynamic
  - ⋆ Ovocyte growth
  - ⋆ Somatic cells Proliferation
- Growth signals from the Ovocyte to somatic cells and *vice-versa*.



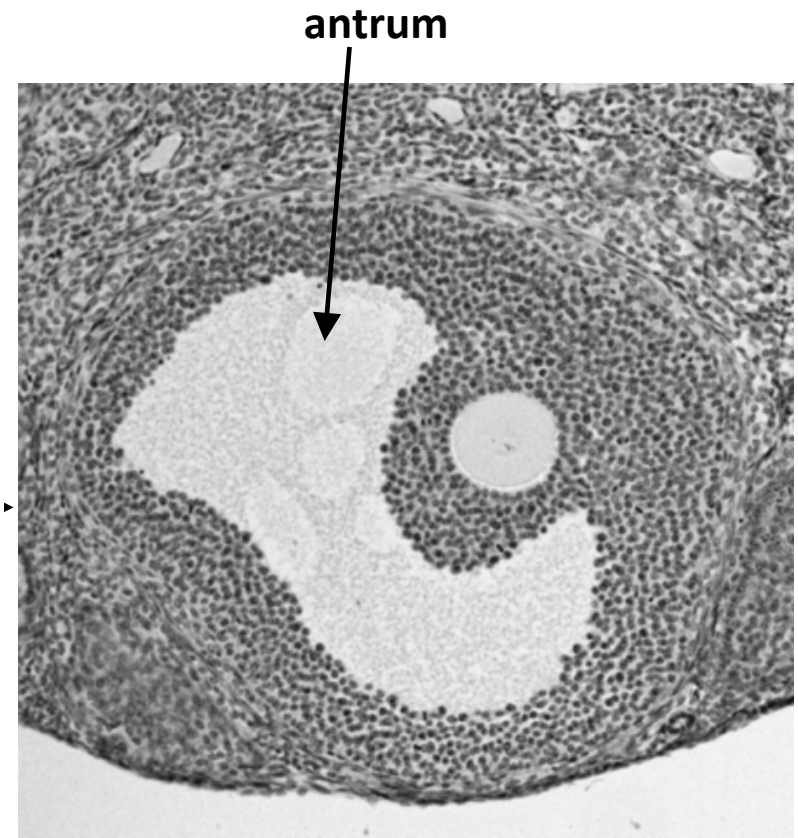
Courtesy of Danielle Monniaux.

Terminal growth



Key features of Follicle terminal growth

- Lost of spherical symmetry
- Joint Dynamic
  - ⋆ Liquid-filled cavity formation and growth
  - ⋆ Switch from proliferation to differentiation of somatic cells
  - ⋆ Morphogen gradient
- **Role of the Liquid-filled cavity ?**

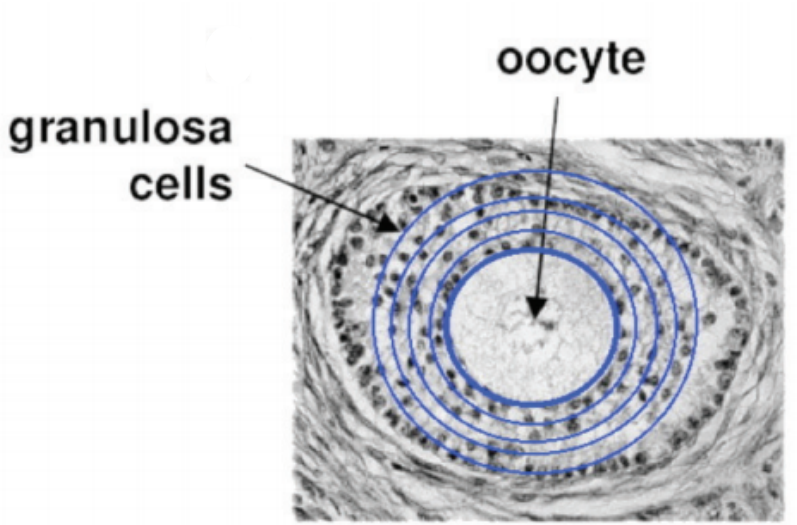


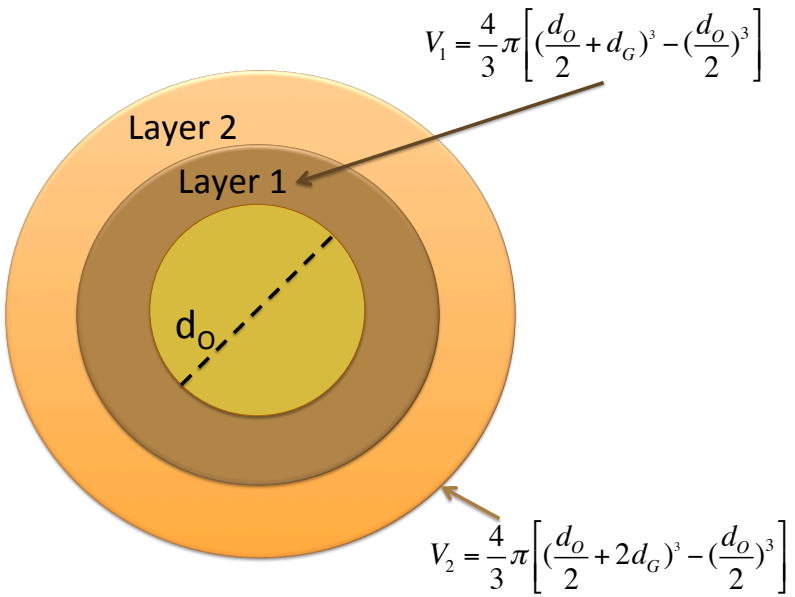
Tertiary (antral) follicle

Simple model : spatial compartment in successive layers

- Spherical ovocyte (d_O)
- Linear proliferation dynamics of somatics cells
- Layer dependent division rate
- Multi-type Bellman-Harris Branching process

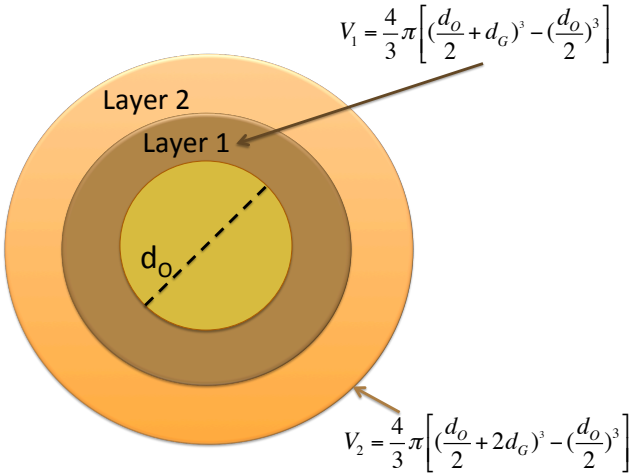
Somatic cells divide and migrate to successive layers.

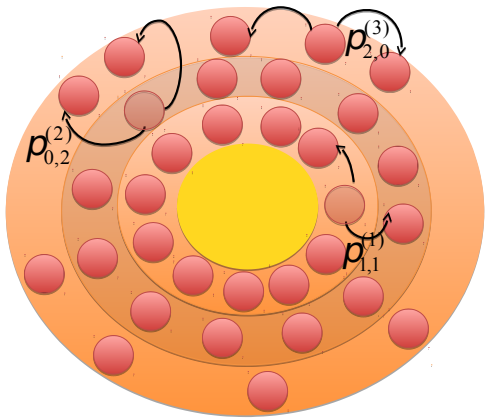




- The geometrical model allows a simple spatial description
- The model is linear and decomposable : exponential growth, with a stable asymptotic spatial profile : there exists a unique $\lambda > 0$ such that the process Z_t verifies

$$\lim_{t\to\infty} Z_t e^{-\lambda t} = \hat{Z} \quad \text{(in law)}$$



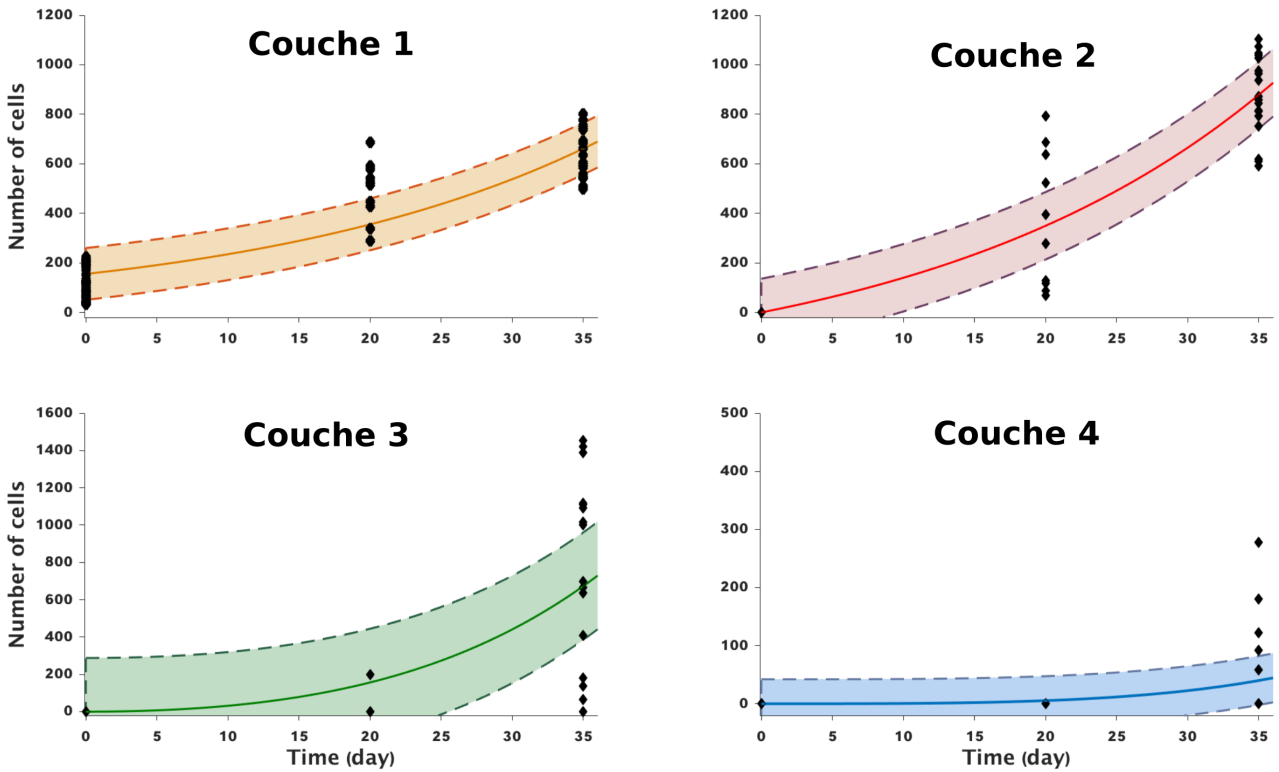


Clément et al. *Analysis and Calibration of a Linear Model for Structured Cell Populations with Unidirectional Motion : Application to the Morphogenesis of Ovarian Follicles*, SIAM App. math, 2019

Fitting results

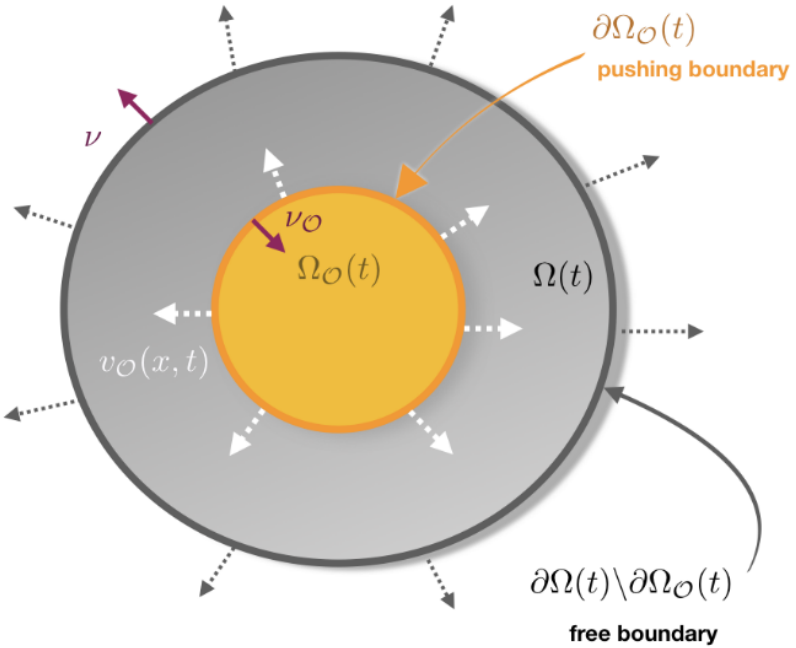
⇒ **Exponential** growth dominated by the first cell layer

⇒ Parameter identifiability and doubling time quantification ($\approx$ 16 days) : Cell-cycle time ↗ with ovocyte distance



Clément et al. *Analysis and Calibration of a Linear Model for Structured Cell Populations with Unidirectional Motion : Application to the Morphogenesis of Ovarian Follicles*, SIAM App. math, 2019

More realistic model ?



$\frac{\partial u}{\partial t} + div\left(\overrightarrow{v}u\right) = b(x)u(t,x)$ for $x \in \Omega(t)$ and with $\overrightarrow{v}$ linked to the negative gradient of the pressure, and the pressure related to the density...
Under locally constant density and spherical geometry, one have :

$$\frac{d}{dt}\left(r_F(t)\right) = \gamma \int_{\Omega(t)} b(x)dx + \frac{d}{dt}\left(r_O(t)\right)$$

work in progress...

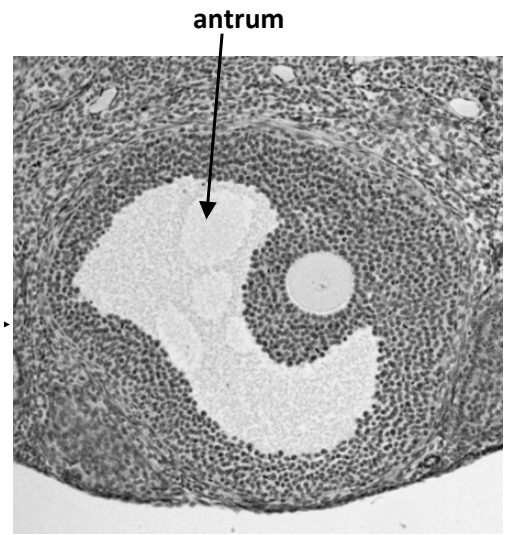
Antrum growth model

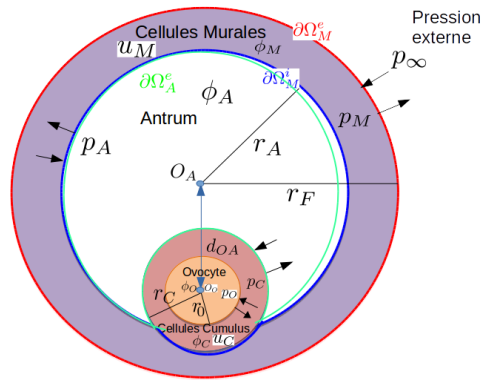
- Multiphasic advection-diffusion-reaction PDE

$$
\begin{aligned}
(\partial_t + \mathrm{div_x}(\mathrm{v_M}\cdot))\, u_M &= R_M \\
v_M &= -\mu_M \nabla_x p_M\,, \\
p_M &= C_M (u_M - u_0)^{\gamma_M}\,, \\
(\partial_t + \mathrm{div_x}(\mathrm{v_a}\cdot))\, \Phi_a &= D\Delta\Phi_a + R_a \\
\mathrm{div_x v_a} &= 0\,, \\
\nabla\Phi_a \cdot \overrightarrow{n}_a &= s(t) = \kappa \int_{\Omega_M} u_M(t,x)dx \\
\frac{d}{dt}\left(\frac{4}{3}\pi r_a(t)^3\right) &= J_{H_2O} = L_p(t)\,(\Delta\Pi - \Delta p) \\
\Delta\Pi &= c_a \Phi_a^{\gamma_a} \\
\Delta p &= p_M(t, \mid x \mid = r_a^+) - p_e \\
L_p(t) &= \frac{\Pi(r_F(t) - r_a(t))^4}{8\eta e(u_M)}\, n(u_M)\,,
\end{aligned}
$$

+ Boundary conditions and constitutive laws

work in progress...





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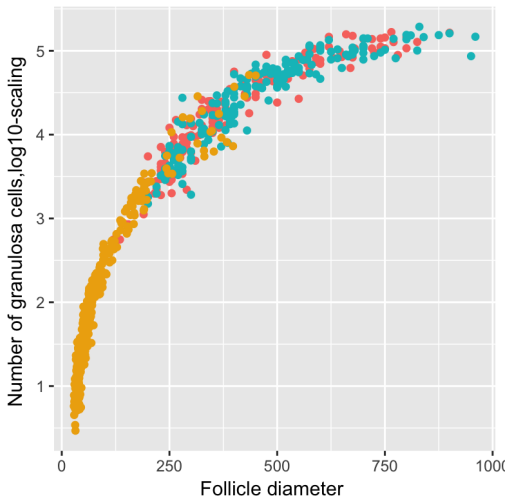


+ Boundary conditions and constitutive laws

work in progress...

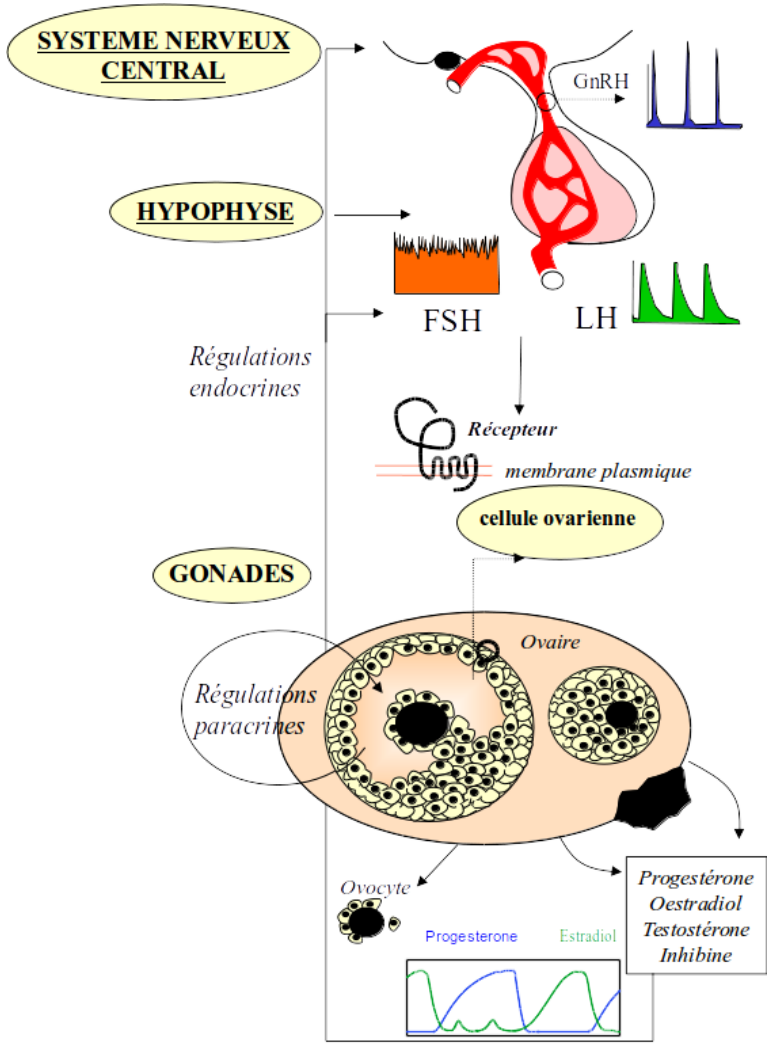
The Mammalian female reproductive system : a complex multiscale system

Encoding and decoding neuro-hormonal signals

Population dynamics : gametogenesis

Intra-cellular level : signaling networks

Yvinec et al., *Advances in computational modeling approaches of pituitary gonadotropin signaling*, Expert Opinion on Drug Discovery, 2018.

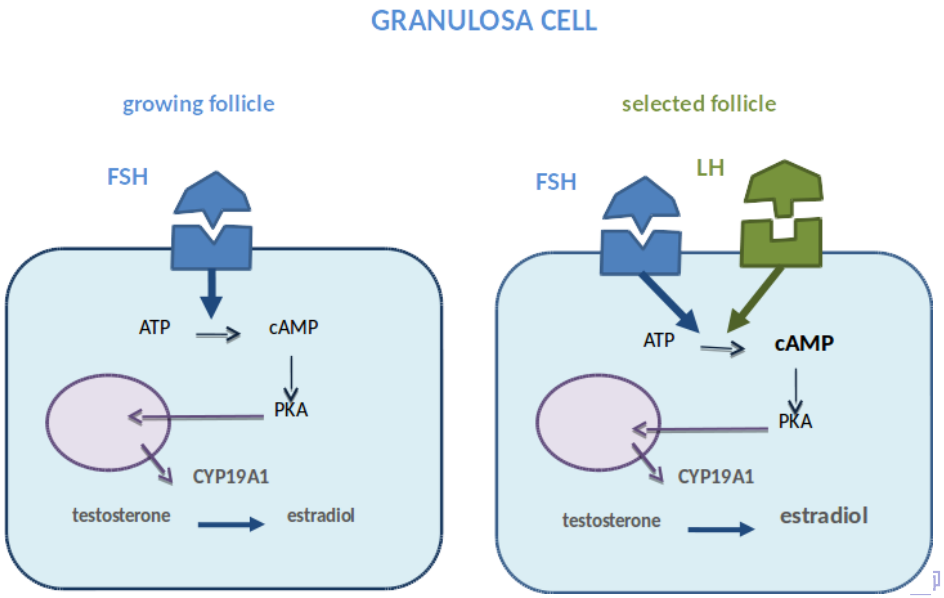


cAMP-induced FSH and its regulation at the cellular level

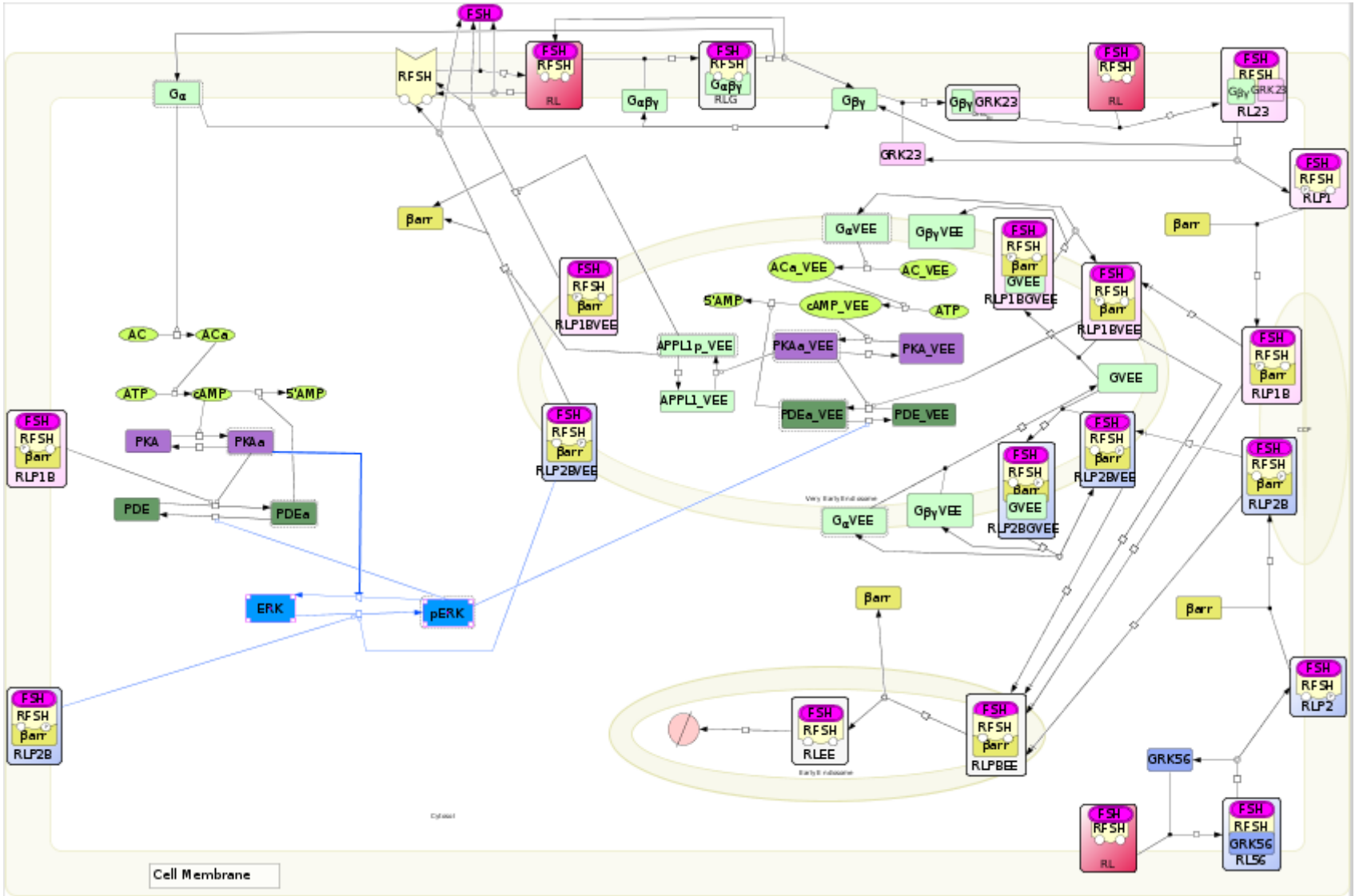
- FSHR signaling network and short-term cAMP induction.
- Long-term regulation of the FSHR network during follicular selection.

$\Rightarrow$ The Cellular "switch" is a pre-requisite for follicle selection .

$\Rightarrow$ This switch is implemented at molecular level by the FSHR network and cAMP output (which is a good marker of follicle maturity).



FSHR networks : very complicated dynamics !



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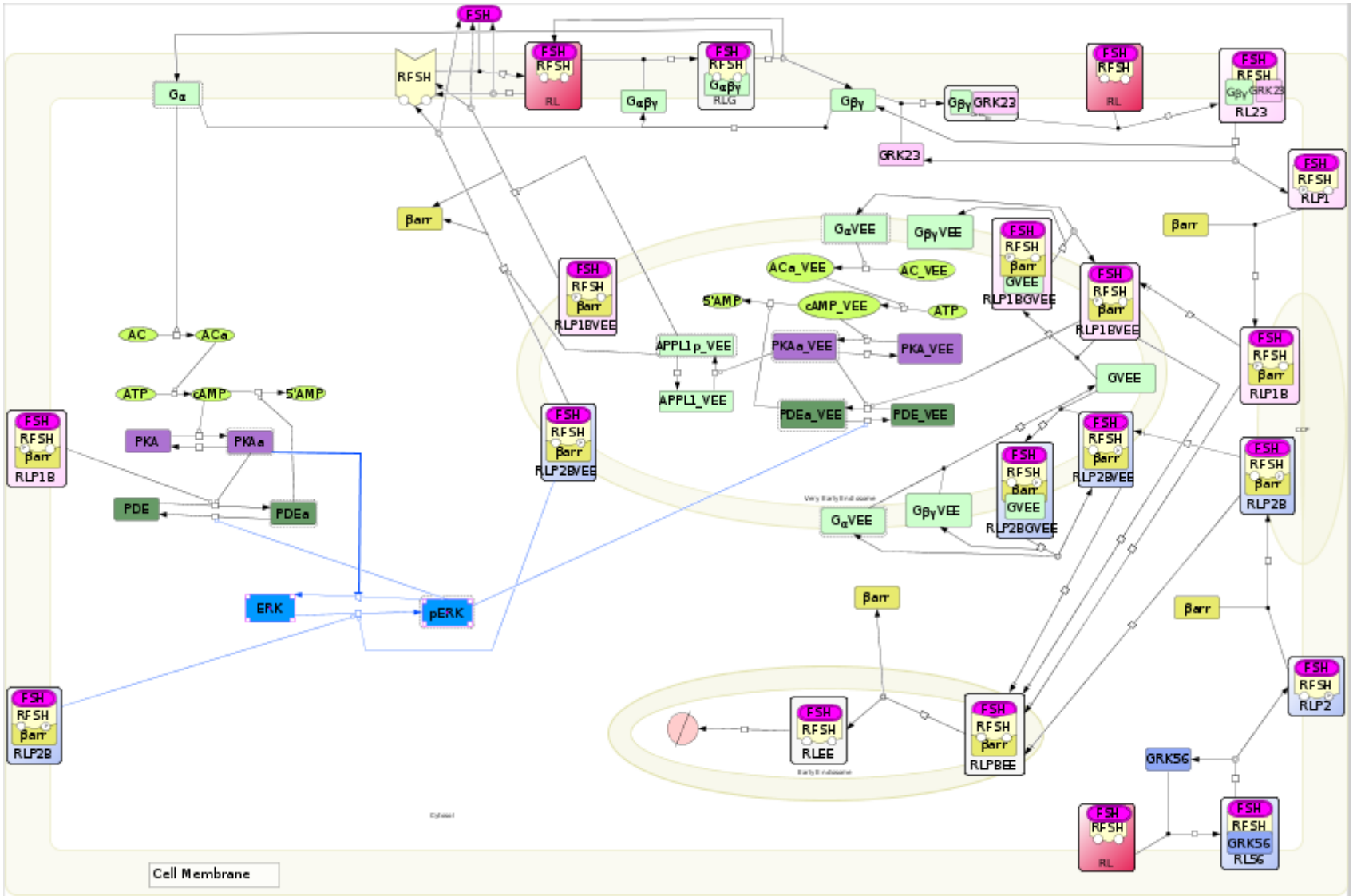
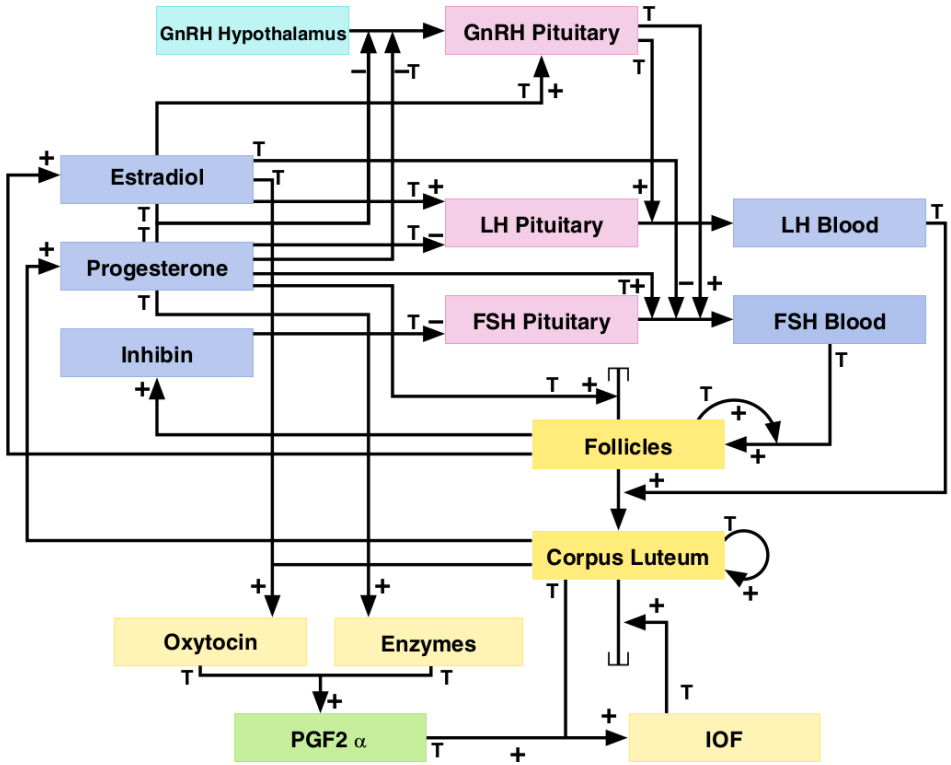


"Network Biology"-> next week !

Summary

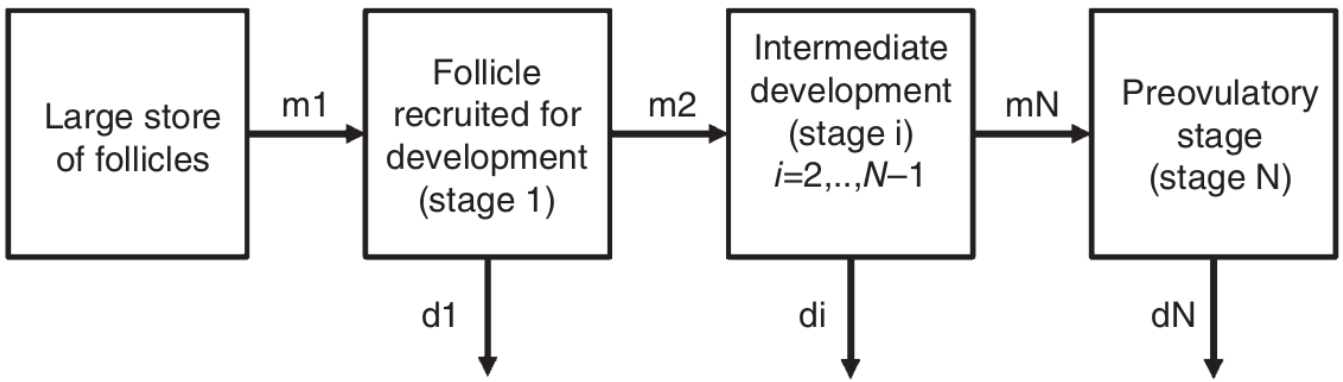
- Circulating hormones dynamical models (Selgrade's model)
  - ⋆ Purely hormonal dynamics
  - ⋆ limit cycles in compact delay differential equation models of the ovarian cycle



Stötzel et al., Therio. 2012

Summary

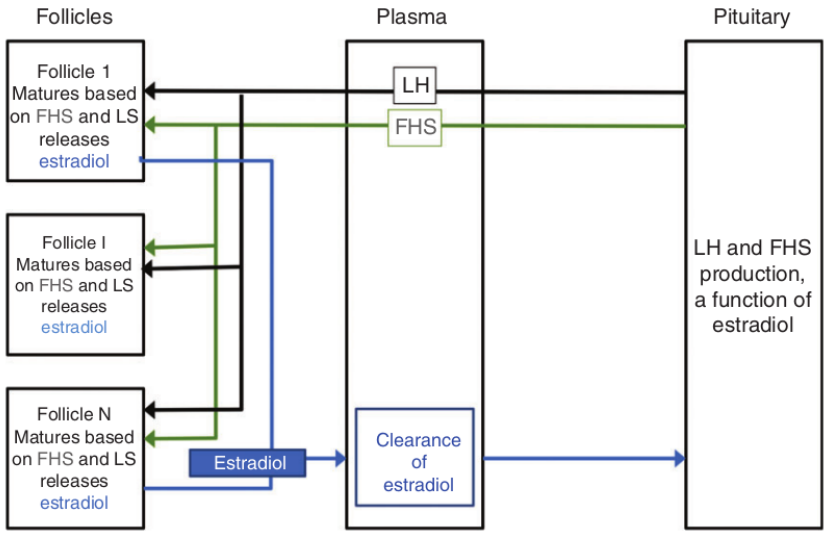
- Circulating hormones dynamical models (Selgrade's model)
- Follicles dynamics in compartment (Faddy's model)
  - ⋆ Reproductive lifespan timescale
  - ⋆ Follicle communication and "hormonal control" through population feedback



Clark & Kruger, WIREs Syst Biol Med 2017

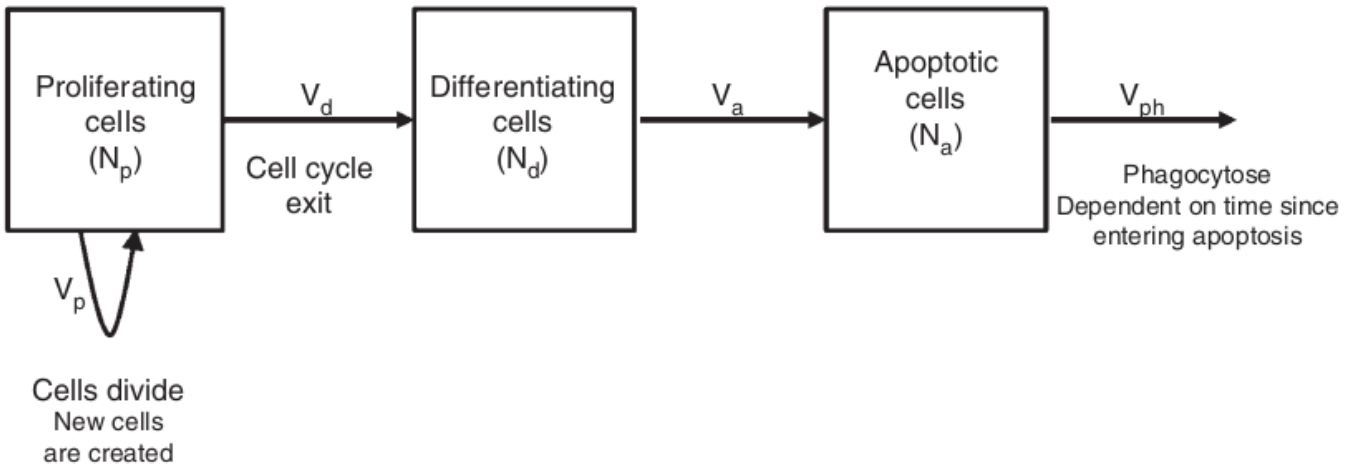
Summary

- Circulating hormones dynamical models (Selgrade's model)
- Follicles dynamics in compartment (Faddy's model)
- Coupled Hormonal/Follicle dynamical models (Lacker's & Clément's model)
  - ⋆ Ovarian cycle / follicle cohort timescale
  - ⋆ Follicle cohort subject to a shared hormonal environment
  - ⋆ The individual follicle maturity rate has local positive feedback and global negative feedback.



Summary

- Circulating hormones dynamical models (Selgrade's model)
- Follicles dynamics in compartment (Faddy's model)
- Coupled Hormonal/Follicle dynamical models (Lacker's & Clément's model)
- Cell dynamics in a single follicle (Clément's model)
  - ⋆ Cell cycle time scale
  - ⋆ Pool of different cell types within a single follicle
  - ⋆ Complex geometry and moving boundary problems



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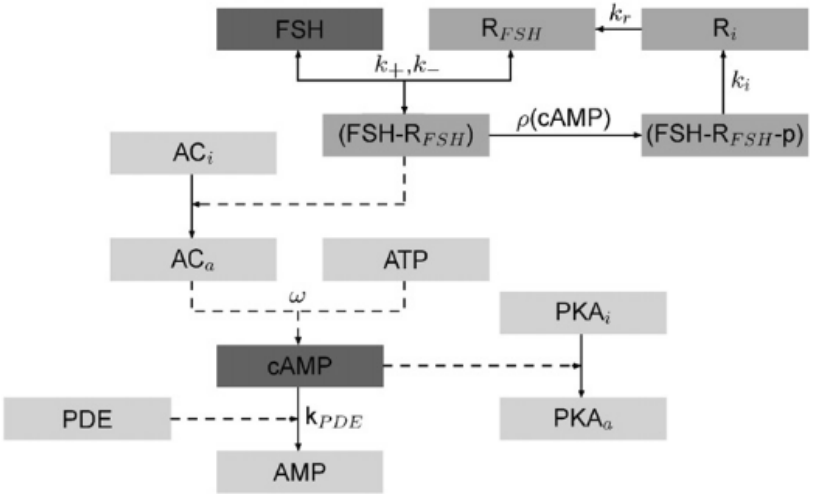
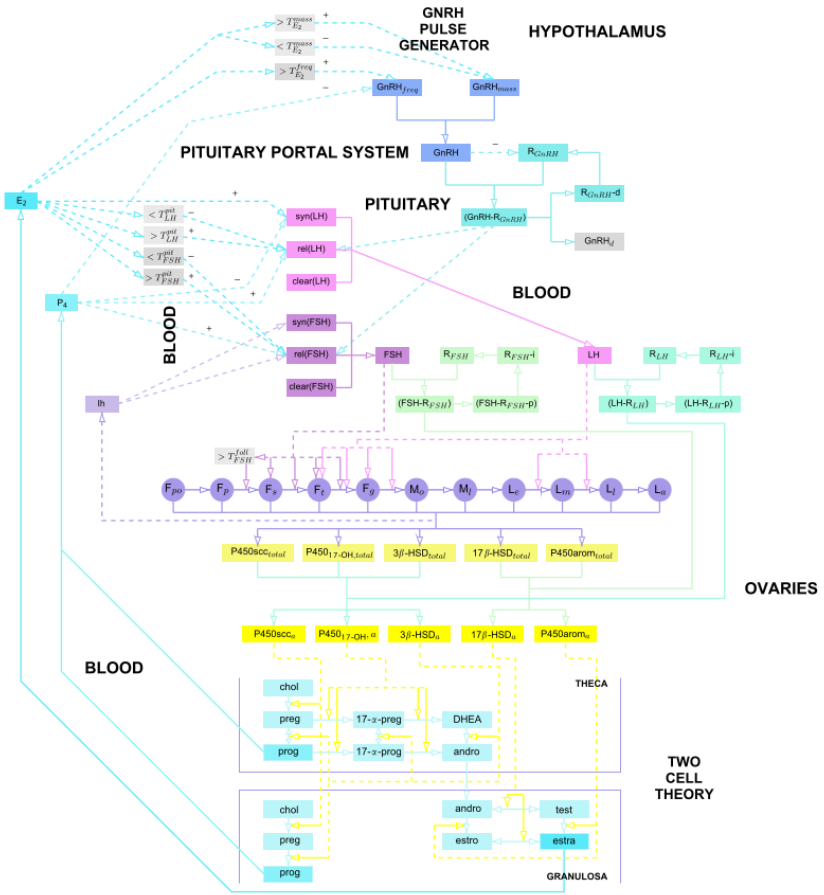
- Cell dynamics in a single follicle (Clément's model)
- Intra-cellular dynamics (Clément / Quignot & Bois)
  - ⋆ Steroidogenesis, cAMP response



Reinecke & Deuflhard,JTB 2007

Multiscale Models of ovarian follicle selection

- Putting "many" pieces together (Reinecke & Deuflhard)



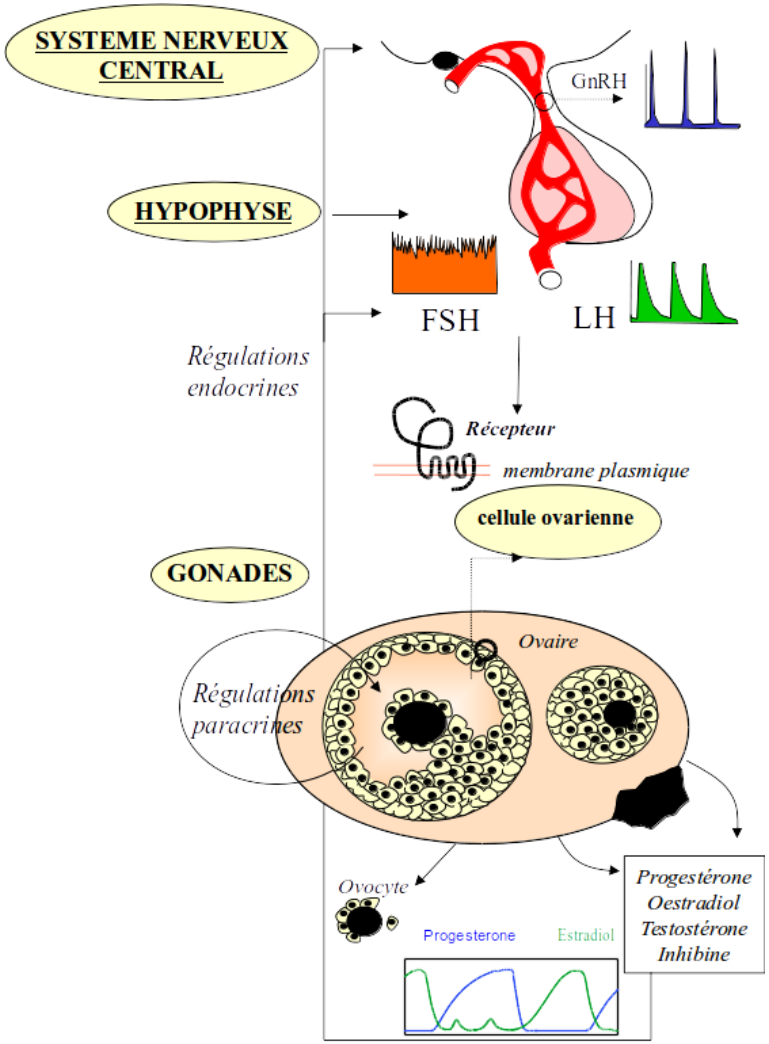
- ⋆ From (stochastic) GnRH pulse generator to detailed steroid metabolism through (compartment-based) follicle development
- ⋆ *Focus in this paper is on the model development*
- ⋆ 43 equations (stochastic input and delay differential equations), 191 parameters.

Reinecke & Deuflhard,JTB 2007

Summary

Population dynamics in ovarian folliculogenesis

- Somatic cells proliferation, differentiation, and migration during follicle initiation& growth
- Multiscale nonlinear dynamics shape the follicle population distribution into different maturity stages.



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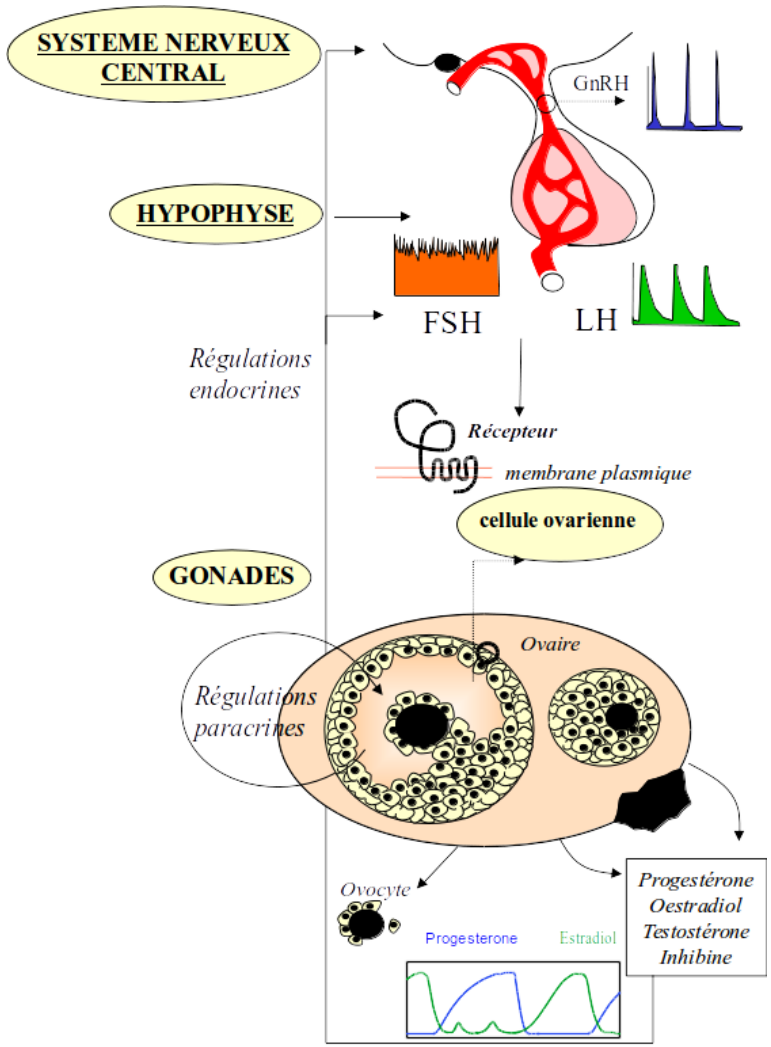
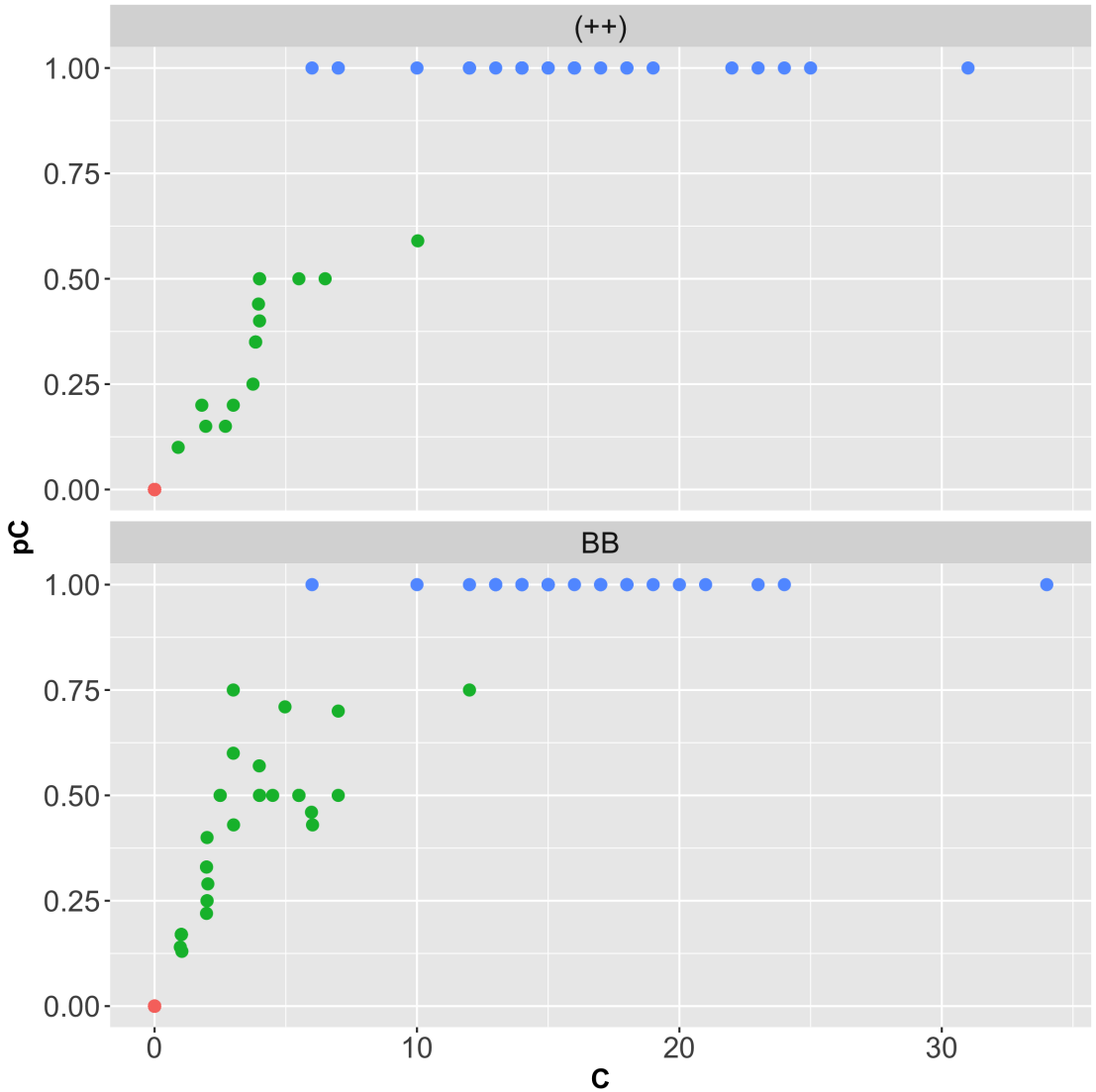


Thank you for your attention !

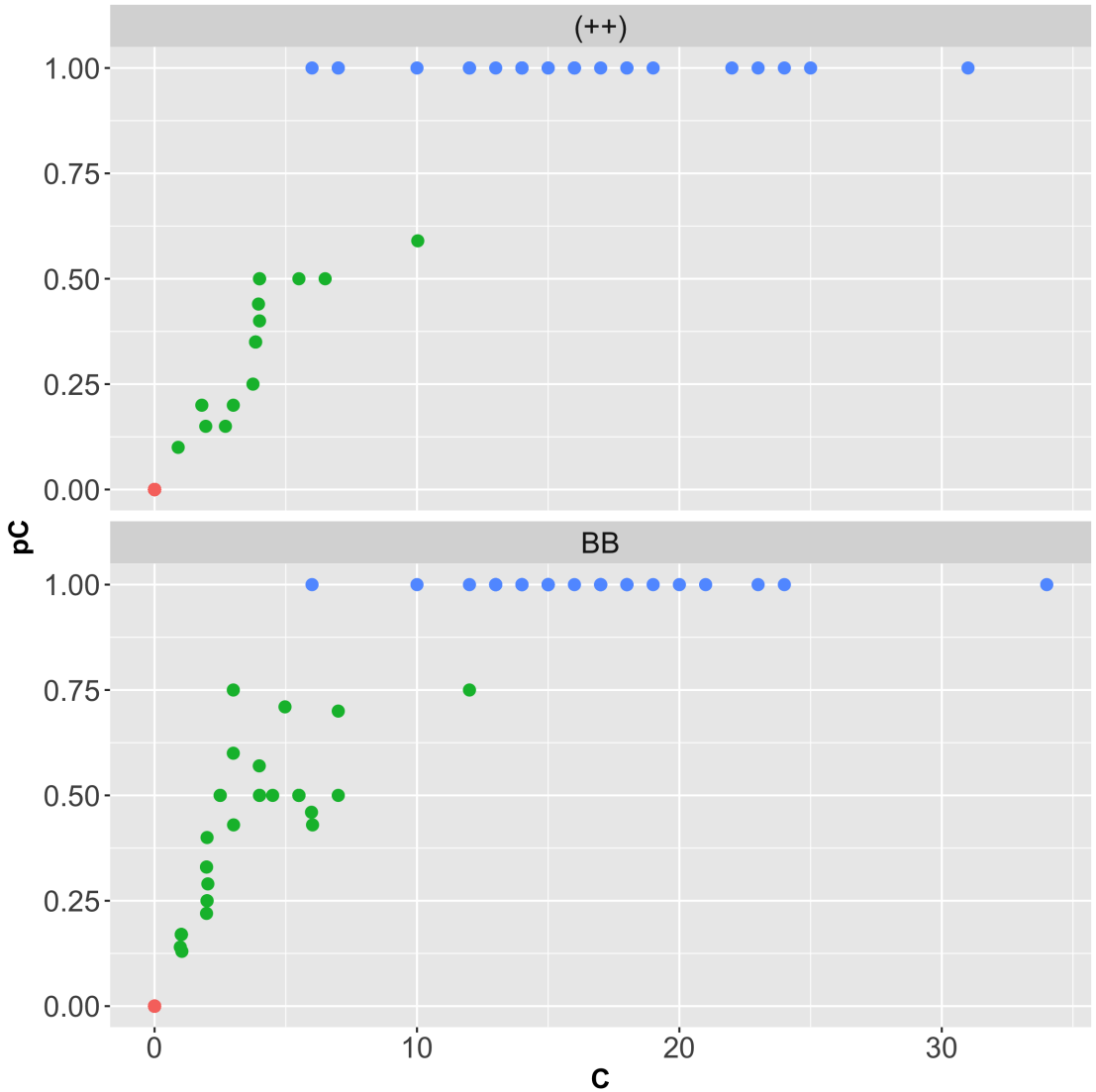
Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus (Courtesy of K. McNatty) : WT (++) vs Mutant (BB)

$\Rightarrow$ **Proportion of cuboid cells** $p_C = C/(F + C)$ **vs number of cuboid cells** C

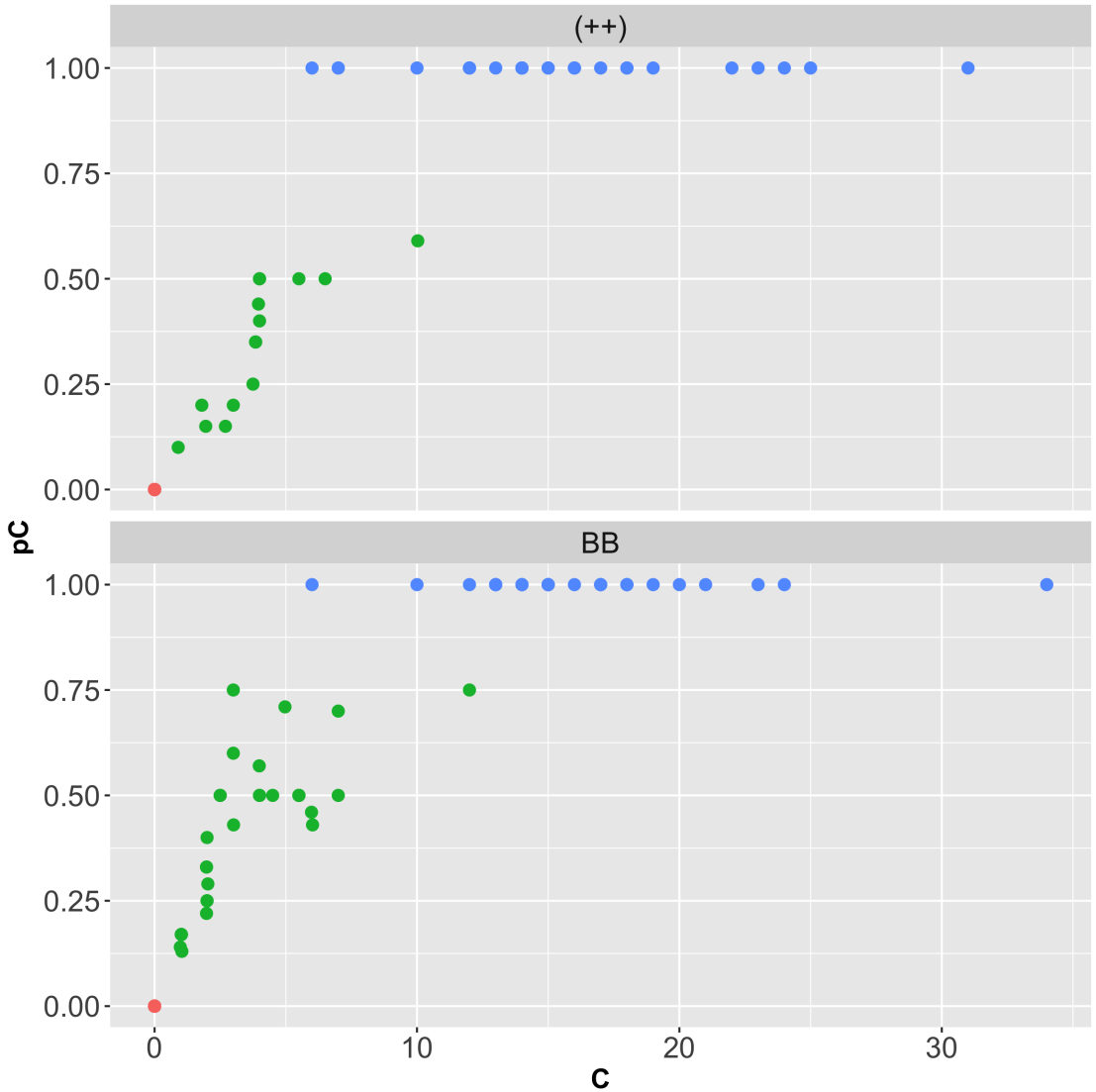
Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus WT vs BB
- Once activated, follicles have "fast" cell proliferation

$\Rightarrow$ **Are both differentiation et de proliferation process concomitant or successive ?**

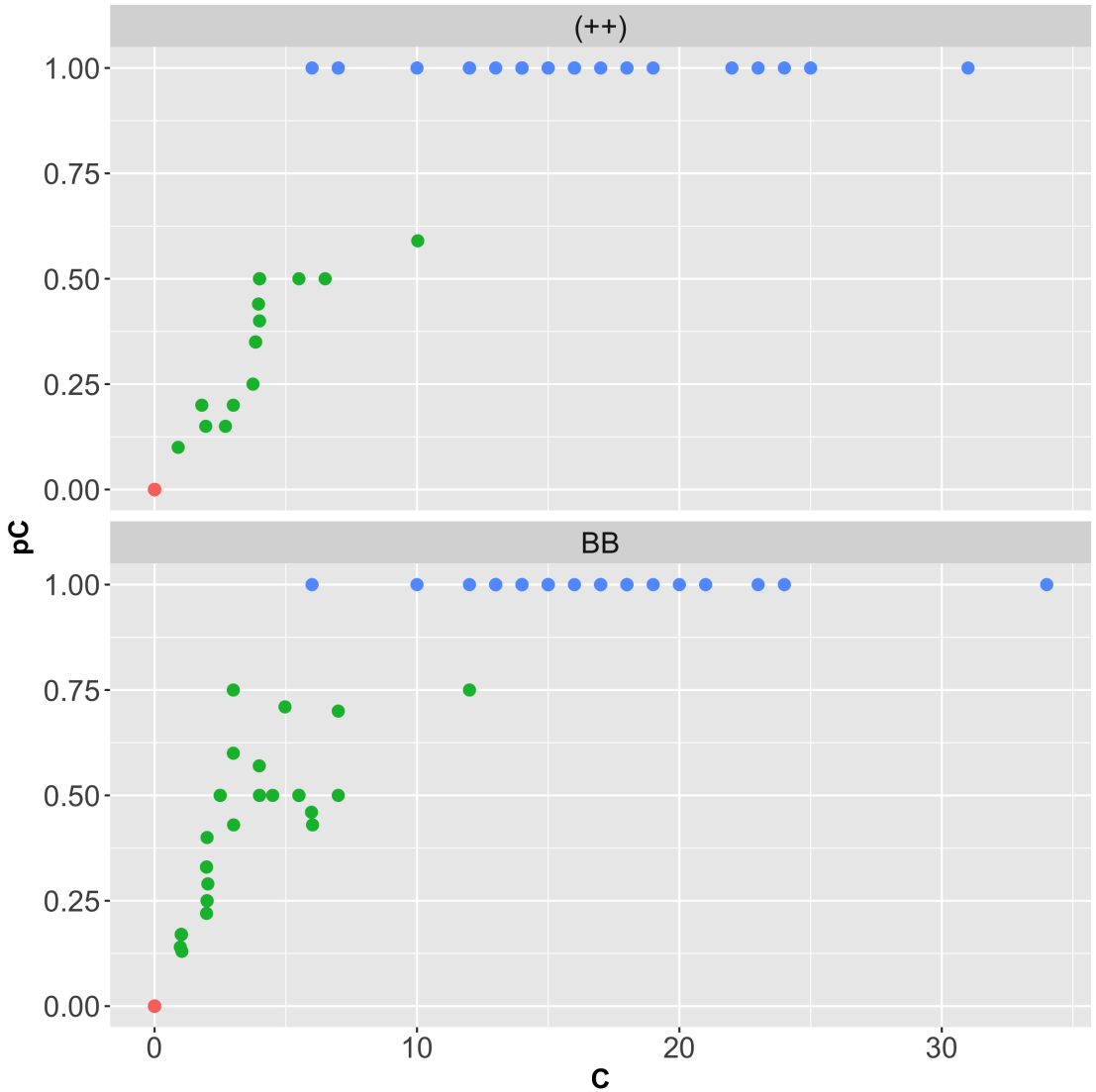
Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus WT vs BB
- Proportion of cuboid cells seems higher in mutant than WT, for a given number of cuboid cells.

$\Rightarrow$ **Is it coming from a kinetic difference ?**

Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus WT vs BB
- Regulatory mechanism for this process are barely known.

$\Rightarrow$ **Is the transition of cell differentiation abrupt or more progressive ?**

Events	Reaction	Intensity function
differentiation	$F \to C$	$\alpha F + \beta \dfrac{FC}{F+C}$
prolifération	$C \to C + C$	γC

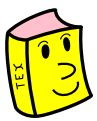
↪ Two cell populations : F (flattened) and C (cuboid)

↪ Small number of cells

↪ Retro-action of cuboid cells on the differentiation rate : is it relevant ?

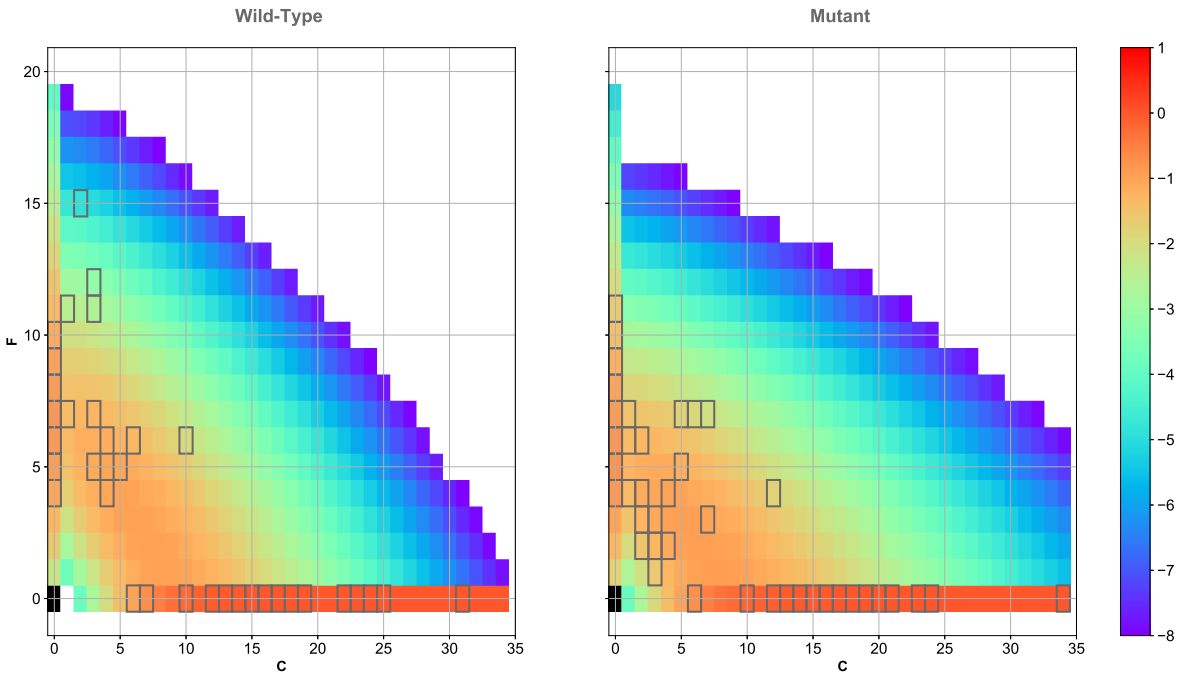
↪ From $(F_0, 0)$ to $(0, C_\tau)$

- Theoretical study
  - $\Rightarrow$ Statistics of the "transition" time τ to reach $F = 0$.
  - $\Rightarrow$ Variability of final cuboid cells ($\mathbb{E}\left[C_\tau\right] < \infty$ if $\gamma < \alpha + \beta$)
  - $\Rightarrow$ Impact of parameters e.g. on qualitative dynamics (progressive vs abrupt)
- Parameter calibration : lack of identifiability. Either $\gamma << 1$ and β unconstrained, or $\gamma > 1$ and $\beta/\gamma >> 1$



Robin et al. *Stochastic nonlinear model for somatic cell population dynamics during ovarian follicle activation*, (submitted) arXiv :1903.01316

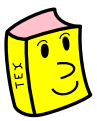
Agreement to data



⇒ The model can capture both data sets

⇒ Lack of identifiability (non-conclusive on retro-action)

⇒ First differentiation, then proliferation (sligtly more concomitant in mutant case)



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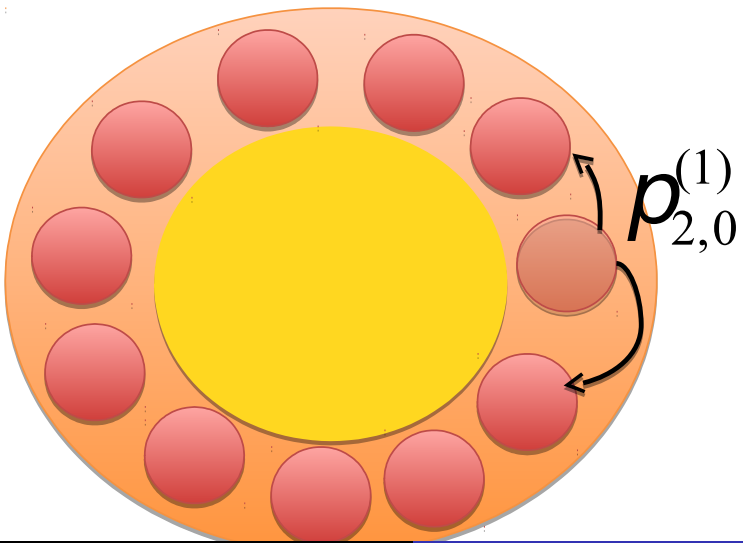
Dynamical model (Multi-type Bellman-Harris Branching process)

- **Age** and **position** dependent division rate (cell cycle regulated by the ovocyte)
- At division, unidirectional motion **centrifugal**
- Cells are **independant** between each other (Unlimited layer capacity)



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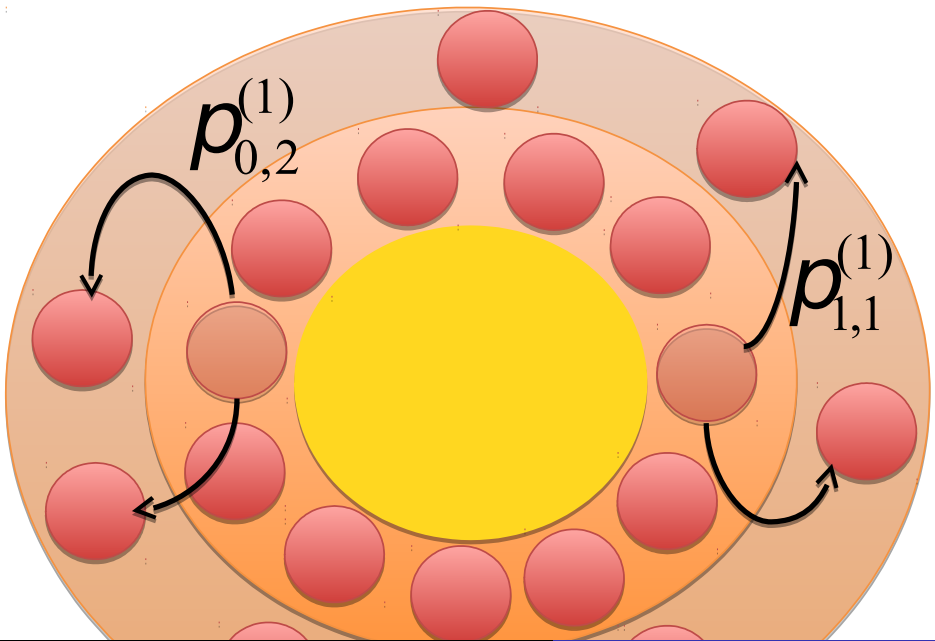

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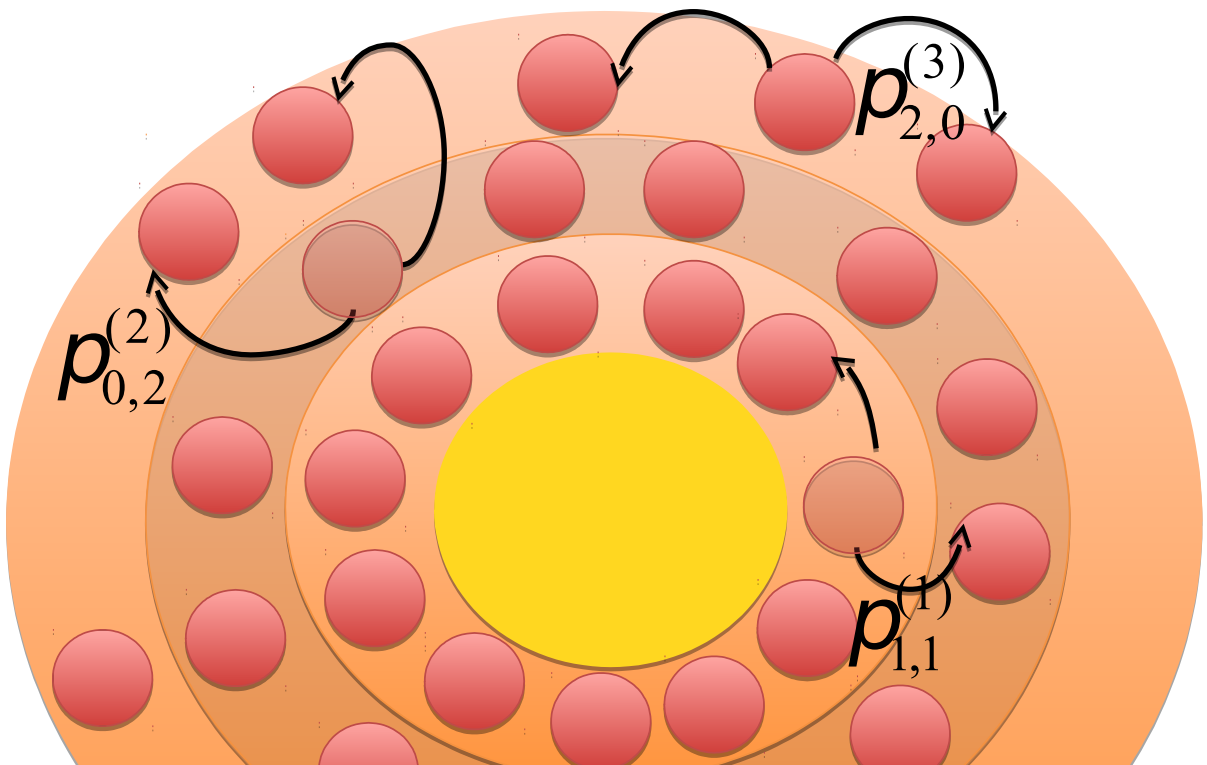
- **Age** and **position** dependent division rate (cell cycle regulated by the ovocyte)
- At division, unidirectional motion **centrifugal**
- Cells are **independant** between each other (Unlimited layer capacity)



Data

- We have counting data of somatic cells in snapshot data, morphological data (diameter) and *order of magnitude of transit times between follicle "type"*

	$t = 0$	$t = 20$	$t = 35$
♯Data points	34	10	18
Total cell number	113.89 ± 57.76	885.75 ± 380.89	2241.75 ± 786.26
Oocyte diameter (μm)	49.31 ± 8.15	75.94 ± 10.89	88.08 ± 7.43
Follicle diameter (μm)	71.68 ± 13.36	141.59 ± 17.11	195.36 ± 23.95

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$\Rightarrow$ Can we explain proliferation in concentric layers by a simple model of "division-migration"? Or do physical constraint play important role ?

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$\Rightarrow$ Can we characterize the growth rate of a follicle and spatial repartition of somatic cells ?

$\Rightarrow$ What is the impact of spatial position of a somatic cell on its division rate ?